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Outcome of Empirical Treatment Change In Patients Failing Antiretroviral Treatment

KEYWORDS: antiretroviral treatment, treatment failure, empiric treatment change

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ABSTRACT *Background: In resource limited settings when resistance testing is often not available a good treatment history can help in quantifying suboptimal drug exposure and anticipating nature of resistance. Material & Methods: In this observational study of 25 patients failing antiretroviral therapy the effective drug exposure was calculated after taking into consideration adherence, appropriateness of prescriptions and kinetic interactions. Treatment was modified and patients were followed up. Results: Of the 25 patients, 23 had virological failure, 21 immunological failure and 14 clinical failure. Possible reasons for failure were non adherence in 16, improper prescriptions in 4 and drug interactions in 4. Following treatment change CD4 count increased by a mean of 127 cells/µl and 11 out of 25 patients had fully suppressed viral loads. Discussion: Despite certain limitations, our results show that, empiric treatment changes based on a comprehensive drug history followed by good adherence leads to a good treatment outcomes.*

INTRODUCTION: HIV infected patients may fail therapy due various reasons including incomplete adherence, inappropriate prescriptions, interacting drug therapy or primary drug resistance. Thus resistance to antiretroviral drugs is an inevitable consequence of long term HAART. Thus it would be appropriate that changing therapy should be best done on the basis of drug sensitivity/resistance profile, but even this approach has its own limitations. An alternative approach is to collect complete history of previous treatments, looking for possible drugs interactions can help in anticipating resistance and changing treatment empirically especially in resource limited settings. We therefore studied the outcome of empirical treatment change in patients failing antiretroviral treatment. The present study was conducted with the objective to determine the factors related to suboptimal drug exposure and outcome of changed empirical treatment.

Material and Methods:

Study type: This was a cross sectional study. Source Population: All the patients enrolled at our treatment centre for anti-retro viral therapy. reatment. and failing antiretroviral treatment. Sample Size: all the patient fulfilling the inclusion criteria during the period of study observational study of 25 consecutive patients who were failing antiretroviral therapy. Case definition: Definition of failure of therapy was based on clinical, immunological, virological parameter and on a combination of these. A comprehensive history of clinical progression of the disease and the treatment taken was sought. Adherence to the antiretroviral therapy which was self reported by the patient was recorded. Improper prescriptions were noted and interacting drugs were identified from available prescription slips. We have attempted to quantify their effects on drug exposure by considering the kinetic interactions. For example, rifampicin is known to reduce nevirapine levels by as much as 58% (3). Therefore it was considered that the patient had 42% drug exposure to nevirapine while on rifampicin. Also, inappropriate prescription involving monotherapy or dual therapy was noted. If only 2 drugs of 3 were prescribed, drug exposure was considered as 67% for that period of time. The effective drug exposure over the entire treatment duration was calculated after taking into consideration all these factors. We considered slabs of 0-15%, 16-53%, 54-73%, 74-94% and 95-100% for adherence on the basis of a previous study (4).

Since the relationship between drug exposure and resistance is bell shaped, it was anticipated that low (<50%) or high level (>90%) of drug exposure would be associated with low levels of resistance (5). Such patients would be expected to do well with the original regimen at least in short term. On the other hand, drug exposures between 50-90% would be associated with a high likelihood of resistance. Lamivudine and NNRTIs have low genetic barrier to resistance and there is complete cross resistance between the NNRTIs (6). These factors were taken into account in anticipating resistance and changing treatment empirically.

Treatment was changed empirically and patients were followed up for periods varying from 3 months to 1 year. They were assessed for clinical improvement by weight gain, immunological and virological parameters.

RESULTS:

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Our study included 25 patients failing antiretroviral therapy. Of these 25 patients 23 had virological failure and immunological failure was seen in 21 patients. Signs of clinical failure were evident in 14 patients (Table 1).

The possible reason for failure in study patients was non adherence in 16 patients, improper prescriptions in 4 and drug interactions in 4 patients. One patient failed despite reported full adherence and appropriate prescription (Table 2).

Table 4 details individual study patient details including previous treatment, effective drug exposure, anticipated resistance to drugs, changed regimen and results of proven resistance wherever available. Genotypic resistance testing could be done in 5 of these 25 patients and the results correlated 100% with the anticipated resistance to various drugs.

Patients were counseled regarding importance of adherence to antiretroviral drugs prior to treatment change. Reported adherence was 100% after treatment change.

Following change in the antiretroviral treatment the weight of these patients increased by a mean of 2.14 kgs. The CD4 count after treatment change were >500 cells/µl in 4 patients, between 200-500 cells/µl in 11 patients and <200 cells/µl in 10 patients. There was an increase in CD4 count from a mean of 151 cells/µl before treatment change to 278 cells/µl after treatment change (table 5).

After change of treatment, 11 out of 25 patients had fully suppressed viral load of <53 copies. Viral load was between 54-10000 in 6 patients, 10000-100000 in 5 patients, while 3 patients had viral load of >100000 copies/µl.

Discussion:

Of the 25 study patients 23 had virological and 21 had immunological failure whereas, clinical failure was evident in 14 of them. This underscores the fact that laboratory monitoring of CD4 counts and viral loads is of utmost importance in detecting early treatment failure in patients with HIV. There were 2 patients who had a viral load of <53 but had immunological failure, clinical progression and were clearly on suboptimal treatment. It is possible that presence of M184V mutation might have prevented the rise in viral load, although resistance must be present in these patients.

Although it was found that in 16 of patients the possible cause of failure was non adherence to therapy, 8 patients had inappropriate prescriptions and drug interactions as a cause of failure. These circumstances may be peculiar to our setting where the physician and patient education programs are suboptimal. One patient failed despite appropriate treatment and full adherence possibly as an inevitable consequence of long term HAART.

Current guidelines recommend resistance testing to optimize drug selection after treatment failure. However resistance tests require a resistant viral population of more than 10-20% to detect resistance. They may not predict hypersusceptibility or efficacy of combinations and boosting (2). Finally, the resistance tests are expensive and are not generally available. Resistance tests could be performed in 5 patients. It was observed that the results correlated well with the drugs to which the resistance was anticipated.

The study has several limitations. The adherence in this study was self reported by the patients. Although the optimal way to assess adherence to antiretroviral therapy is not known, self reported adherence appears to be the most feasible method (7, 8). Since this was an observational study CD4 levels and viral loads were not always done at the same laboratory. The consequence of poor adherence might be different when the viral load was expected to be high than when it was low. This might have important implications for anticipating resistance in that one might give a different weight to early non-adherence as compared to late non-adherence. This factor could not be taken into consideration in this study. Patients with very low or high levels of drug exposure were continued on the initial treatment assuming that they would do well in the short term. However, long term follow up may reveal failure due to archived resistant mutations.

Despite these limitations our results show that in patients failing antiretroviral therapy empiric treatment change followed by good adherence and drug exposure leads to good clinical, immunologic and virological outcome.

Table 1. Type of failure in study patients

No.	Type of failure	No. of patients (n=25)
1.	Clinical only	00
2.	Immunological only	01
3.	Virological only	02
4.	Clinical + Immunological	01
5.	Clinical + Virological	02
6.	Immunological + Virological	08
7.	Clinical + Immunological + Virological	11

Table 2. Possible reasons for failure in study patients

No.	Reason	No. of patients (n=25)
1.	Nonadherence	16
2.	Inappropriate prescriptions	04
3.	Drug interaction	04
4.	Long term HAART	01

Table 3: Total drug exposure in study patients

No.	Total drug exposure (%)	No. of patients (n=25)
1.	00 – 15	04
2.	16 – 53	03
2.	54 – 73	06
3.	74 – 94	05
4.	95 – 100	07

Table 4. Individual study patient details

No.	Previous treatment	Effective drug exposure (%)	Anticipated resistance	Changed regimen	Proven resistance
1.	ZDV+3TC+EFV	86	3TC+EFV	ZDV+3TC+EFV	
2.	ABC+ZDV+EFV	100	Nil	TDF+3TC+d4T+LPV/r	

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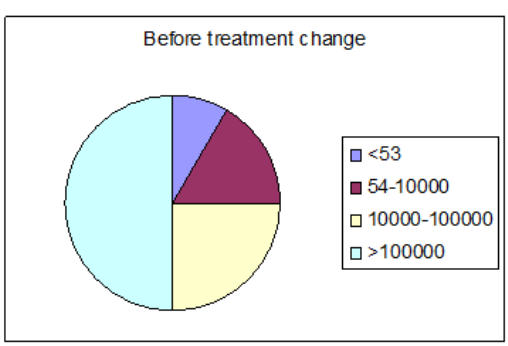
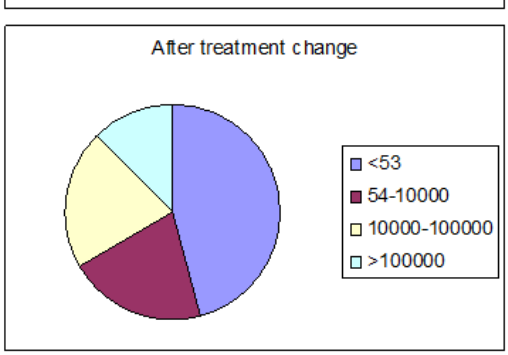
3.	ZDV+3TC+EFV	70	3TC+EFV	ZDV+ddI+LPV/r	M184V,Y181C,G190A,K101E,L63P, M36I
4.	d4T+3TC+EFV	50	3TC+EFV	ddI+3TC+IDV/r	
5.	ZDV+3TC+NVP	12	Nil	ZDV+3TC+NVP	Nil
6.	ZDV+3TC+NVP	91	Nil	ZDV+3TC+EFV	
7.	ZDV+3TC+EFV	43	3TC+EFV	ZDV+3TC+EFV	
8.	ZDV+3TC+EFV	97	Nil	3TC+d4T+EFV	
9.	ZDV+3TC+d4T+EFV	98	Nil	ABC+3TC+EFV	V106M,G190A,M184V,L74V
10.	ZDV+3TC	6.6	Nil	ZDV+3TC+NVP	
11	ZDV+3TC+IDV	63	3TC	ABC+3TC+IDV/r	
12.	ZDV+3TC+EFV	98	Nil	ZDV+3TC+EFV	
13.	ZDV+3TC+NVP	80	3TC+NVP	ZDV+3TC+EFV	
14.	ZDV+3TC+NVP+EFV+d 4T+ddI+IDV+LPV/r	55	3TC+EFV+NVP	d4T+3TC+TDF+LPV/r	
15.	ZDV+3TC+EFV	45	3TC+EFV	3TC+d4T+EFV	
16.	3TC+d4T+EFV	14	Nil	TDF+3TC+EFV	
17.	ZDV+3TC	10	Nil	3TC+d4T+EFV	
18.	ZDV+3TC+EFV	82	3TC+EFV	TDF+ZDV+3TC+LPV/r	M184V,K103N,TAMS
19.	3TC+d4T+NVP	63	3TC+NVP	d4T+ddI+LPV/r	
20.	ZDV+3TC+NVP	65	3TC+NVP	3TC+d4T+EFV	
21.	ZDV+3TC+NVP	80	3TC+NVP	ZDV+3TC+EFV	
22	ZDV+3TC+ATV	100	Nil	ZDV+3TC+EFV	
23.	ZDV+3TC+NVP+IDV/r	100	Nil	TDF+ZDV+3TC+LPV/r	M184V,K70R,D67N,K219,K101E,L90M
24.	ZDV+3TC+NVP	65	3TC+NVP	ZDV+3TC+EFV	
25.	ZDV+3TC+NVP	99.3	3TC+NVP	TDF+ZDV+3TC+LPV/r	

Table 5: Vi5ral loads in study patients

Viral load	Before treatment change	After treatment change
<53	02	11
54 – 10000	05	06
10000 – 100000	06	05
>100000	12	03





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