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Is ALT control really necessary for routine ART monitoring in resource poor settings?

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Background

In Mozambique the reported prevalence of HIV infection in the adult population is of 16.1% (12.5% – 20%), equivalent to 980,000 to 1,700,000 HIV infected people, of which more than **200,000[1] are in urgent need of antiretroviral treatment.**
In Mozambique, like in several sub Saharan countries, access to ART is still very limited (10.8% of the population in urgent need).
To scale up the number of patients on ART, The Ministry of Health of Mozambique has launched a policy of decentralisation of the comprehensive HIV/AIDS care and treatment to peripheral health centres. MSF is supporting the national plan in the Health District of Chamanculo in Maputo (with an estimated population of 300.000).
At May 2006, MSFCH provides care to 5.700 HIV positive people and ARV therapy to 3.275 of them, in a governmental day hospital at district level and using the national guidelines. Aware of unmet needs for treatment, MSF has committed to accelerate and increase inclusions of patients on ART, but this could only go together with the simplification of the national protocols.

In the national treatment guideline, the first-line regimen contains NVP (unless transaminases (ALT) >5x ULN) or EFV for patients in treatment for tuberculosis.
In case of severe hepatic toxicity, defined as an increase of ALT > 5 x ULN during the course of therapy, ART is interrupted and NVP replaced by EFV.
The guideline strongly recommends a regular transaminases assessment before and during the treatment; therefore ALT is checked for all patients eligible for ART at baseline, two weeks after initiation, 1 month and then six monthly, unless abnormalities are encountered.

Performing ALT is very demanding in terms of logistics and costs in resource-poor settings and could be an obstacle to the scaling up policy foreseen by the Ministry of Health and other health partners.

We decided to assess the results in term of impact on patient management and therefore pertinence from a public health perspective of regularly performing ALT, by a retrospective analysis of the cohort followed in the day hospital of Alto Mae, District of Chamanculo and on the files of 19 patients for which ART were interrupted because of hepatotoxicity.

Methods

In MSF service, the patients' files are regularly updated during medical visits and all the data of clinical follow-up are systematically collected using a monitoring software (Fuchia©, Epicentre, Paris, France) that provides automated reports and allows for specific analysis.
Using data routinely collected through Fuchia, we conducted a small retrospective study based on patients' files.

From the cohort of patients who started ART any time from March 2003 to December 2005, we selected all the files of the patients who developed any intolerance that necessitated ART interruption and we focused our analysis on those who presented with elevated transaminase values (normal values11-45 U/l for males and 11-35 U/l for females) justifying a change in the treatment regimen.

For the 19 patients who interrupted ART because of hepatotoxicity, the following variables were analysed: age, sex, clinical and immunological situation at baseline, date of start of ART, baseline ALT, all available values of ALT (after two weeks of treatment - 1 month - 3 months, etc), date of ART interruption, clinical signs at the time of interruption, date of the restart of the alternative treatment.

This information was taken from the patient's files, entered in Epi info software and simple descriptive analysis was done.

Results

In the Day Hospital of Alto Mae, 3.146 patients started ART from March 2003 to December 2005, 2.367 (75%) were still on treatment at the end of the period, with a median follow up of around 12 (IQR: 7-16) months. In the ART cohort, 157 (5%) patients died, 141 (4.5%) had to stop treatment for any reason and 540 (17.1%) were lost to follow up or with missing data.
Out of the 3.146 patients followed from March 2003 to December 2005, 90% were on standard first line D4T/3TC/NVP; the remaining had to shift to another regimen due to contraindications or concomitant tuberculosis.

Of the 141 people who had to stop treatment, the causes were reported for 127 of them:

- 4 (2.8%) for neuropathy,
- 19 (13.4%) for hepatotoxicity,
- 45 (32%) for skin reactions,
- 59 (41.8%) for other allergic reactions

19 cases of drug interruption due to liver toxicity were found, giving a global incidence of 0.6% (0.9% if calculated on patients still in follow up). All these patients, except one were on treatment with a NVP based regimen (1 case on EFV because of concomitant TB)

There were equally male and female in this group of patients.
The median age was 39 (range 25 – 65).
At ART initiation, the distribution of the 19 patients concerning WHO clinical stages was similar to that of the global cohort:

- 1 (5%) in stage 1
- 3 (16%) in stage 2
- 10 (53%)in stage 3
- 5 (26%) in stage 4.

The average Cd4 count was of 91 cell/mm3 (13-280).

As far as ALT values are concerned:

- For the patients who developed severe hepatotoxicity, the median ALT value at the time of ARV initiation was 37.0 (14.0 – 129.0) U/L
- The highest median value of ALT measured after initiation of ART was at 1 month-follow up, and was 308 (0.0-897.0) U/L.
- The median of ALT at interruption of ART was 376.0 (155.0-897.0) U/L.
- The average increase of ALT, from initiation to the date of ART interruption, was 415.8 (126.0-877.0) U/L.
- The median of ALT at the time of shift to the alternative treatment was 55.0 (15.0-235.0) U/L.

As far as the time of interruption is concerned, 52.6% of patients interrupted at 1 month-follow up, cumulatively, 74% of patients had interrupted at 2 months-follow up.

As far as clinical symptoms and signs are concerned:
Thirteen (68.4%) patients who interrupted ART treatment did not have any clinical symptom and sign at the moment of interruption. There were no differences in the baseline median Cd4 values between symptomatic and asymptomatic patients (65 and 99 respectively).

The different clinical signs and symptoms equally presented were: asthenia, jaundice, abdominal pain, liver pain and hepatomegaly.

Conclusions

Despite the small number of patients, our study can give an orientation on the pertinence of the regular monitoring of transaminases for patients on ART.

Only 19 (0.6%) of 3.146 patients who started ART developed severe liver toxicity justifying changes in regimen.

This retrospective study has many limitations: data are routinely collected and do not allow for the analysis of possible other causes of liver problems (eg: co infection with viral hepatitis), patients that are lost to follow up or dead can also have had liver impairment, causing an underreporting of the toxicity.

Our data confirm the increased risk of toxicity in the first 2 months of treatment; an increased surveillance is therefore necessary during this period.

More than half of the patients with severe liver toxicity were asymptomatic. It is therefore important to investigate (through bigger and *ad hoc* studies) risk factors and mild symptoms suggestive of liver toxicity to define new algorithms for the management of hepatic side effects and better target the use of resources in the monitoring of ART toxicity.

Besides specific patients (pregnant women, TB patients or patients symptomatic for liver dysfunction), the pertinence in terms of cost/efficacy of regular ALT tests should be questioned. Simplification of protocols will facilitate follow up of patients on ART in peripheral health structures in resources-poor settings.

(Footnotes)
[1] Source: MISAU, epidemiological survey 2004

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