# Underreporting of side effects of standard first-line ART in the routine setting in Blantyre, Malawi.

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**Abstract**

**Introduction**

In the Malawi ART programme, 92% of 250,000 patients are using the standard first-line regime of stavudine-lamivudine-nevaripine. National ART reports indicate <4% experience ART side effects, much less than expected from literature.

**Methods**

We interviewed adult patients on standard first-line ART for at least one year, after routine visits to an urban clinic in Blantyre, Malawi. We determined the prevalence of symptoms that are common side-effects, described discrepancies between symptoms that patients reported to us and those that had been recorded by attending staff as side-effects in the point-of-care electronic monitoring system, and studied factors associated with such discrepancies.

**Results**

Of 170 participants, 75 (44%) reported at least one symptom, most common were symptoms suggesting peripheral neuropathy (n=57) and lipodystrophy (n=16). Forty-six (66%) symptomatic patients said they reported symptoms to attending ART staff. Side-effects were recorded in the clinic database for just 4 patients. Toxicity recording was too low for meaningful analysis of factors associated with discrepancies between reporting and recording of side-effects. The prevalence of symptoms indicating characteristic side-effects of the standard first-line regimen was 39% based on interviews, and 2% in the electronic monitoring system.

**Conclusion**

There was gross under-recording of side-effects in this setting, mainly due to not recording by ART staff. Pressure of work and insufficient perceived benefit of side-effect recording are suspected causes. Local and national ART reports do not reflect the true toxicity of the standard first-line regimen.

## Introduction

Malawi began rapid roll out of free antiretroviral therapy (ART) in 2004. At the end of 2010 there were around 250,000 patients on treatment. The national ART programme uses a public health approach to ART with a standard first-line regimen consisting of a fixed-dose combination of nevirapine, stavudine and lamivudine and with limited monitoring of toxicities, mainly by clinical means. The vast majority (91%) of Malawian patients use the standard first-line regimen. National ART reports have consistently indicated that the overall prevalence of side effects is 4%[1,2]. However evidence from literature and also our personal experience indicates that toxicities of this regimen are far more common. Peripheral neuropathy and lipodystrophy are frequent side effects of stavudine in western settings and were also highly prevalent in Africans. Peripheral neuropathy varied from 20 to 34% after 1 to 3 years on ART[3-5], and lipodystrophy occurred in one-thirds of Rwandans after 1 to 2 years on ART[6,7]. High lactate syndromes and pancreatitis are serious toxicities associated with stavudine but are relatively rare. Skin rash occurs in around 17%[8] and hepatotoxicity in 1 – 11% of patients initiated on nevirapine, although clinical jaundice is rare[9]. With such discrepancies between literature and national data we postulate that there is under-estimation of side effects in the national ART reports. This could be due to a failure of reporting symptoms by patients during the short, routine clinic visits and/or by failure of health care workers to identify and record certain side-effects. Possible factors related to discrepancies between presence of side-effects and the prevalence thereof in records could be grouped as follows: patient related: age, sex, education level, cultural constraints in patient-attending staff relationship; side-effect related: type, continuity and severity of symptom, and impact on daily activities; health care system related: day of the week (busy clinics), knowledge level and experience of attending staff, language barrier between patient and attending staff.

We did a survey in an urban ART clinic in Blantyre, Malawi, to measure the prevalence of symptoms known to be common side effects of the first-line regimen, to determine discrepancies between symptoms that patients reported and those that were recorded in the routine monitoring system, and to study factors that are associated with such discrepancies.

## Methods

This was a cross sectional study at the busy ART clinic of Queen Elizabeth Central Hospital (QECH) in Blantyre, the major city of southern Malawi. QECH provides primary to tertiary care and is affiliated with the College of Medicine, the only medical school of Malawi. Routine laboratory monitoring of toxicity is not practised. ART reports of QECH indicate that the prevalence of side effects is between 5-7% and that 91% of patients were on the standard first-line regimen at the time of the survey[10]. It is policy at the clinic that patients with symptoms are reviewed by clinicians.

Patients were eligible for enrolment in the survey if they were on the standard first-line regimen for at least 12 months, and were aged 18 or above. There were no exclusion criteria. We approached patients for enrolment after they had completed routine ART visits. We developed a questionnaire to screen for common side-effects associated with the standard first-line ART regimen and for possible reasons for not reporting side-effects to ART staff. Symptomatic patients were categorized into a group that had at least one symptom known to be a common side-effect of the first line regimen (peripheral neuropathy, body shape changes, rash, yellow eyes) and a group that had no such symptoms but had gastro-intestinal complaints, which are less likely to be ART side effects after one year or longer on treatment. Severity of symptoms was self-graded by patients based on DAIDS toxicity tables[11], with the exception of rash and yellow eyes (always classified as severe) and loss of appetite (always mild/moderate). A research assistant, who spoke English and the local language and was not part of the resident ART staff, was trained to administer the questionnaire. Patients could choose their preferred language for completing the

questionnaire. We determined whether there was a language barrier during the ART visit by asking the patient if they spoke English and if they found that the attending ART staff spoke the local language. We did not formally assess language skills.

After the questionnaire was completed, one of the authors extracted data of the ART visit concerning side-effects from the electronic monitoring system. This electronic monitoring system has been described in detail[12] and is used by ART staff (clinicians and nurses) to record symptoms, toxicities and other relevant ART information at the point-of-care. The data were analysed using SPSS version 12.0 software. We used the $\chi$-squared test, Fisher's Exact test, t-tests and the Mann-Whitney U-test to compare continuous and categorical data where appropriate. Since the survey obtained information that is part of routine ART practice and data were collected in an anonymized fashion, we did not obtain informed consent from patients. Publication of the data was approved by the Research and Ethics Committee of the College of Medicine, Blantyre, Malawi.

## Results

The survey was carried out in May – June 2010. All 170 patients whom we approached agreed to participate, 62% were female and the mean age was 38.6 years. In the interviews 75 (44%) patients mentioned a total of 117 symptoms. Pain and numbness of the legs (n=57) was the most common symptom, followed by unwanted changes in body shape (n=16), poor appetite and abdominal pain (both n=10). Rash (n=7) and yellow eyes (n=2) were less frequent. Symptoms more specifically regarded as side-effects of the first-line regimen (peripheral neuropathy, body shape changes, rash and/or yellow eyes) were present in 89% of symptomatic patients. Twenty-five patients had at least one severe symptom. Age, gender, education level, duration of ART and WHO clinical stage at the start of ART were not associated with being symptomatic. Not surprisingly since this is a policy at the clinic, symptomatic patients were more frequently attended to by clinicians compared to those without complaints. As a result, there was a borderline significantly higher prevalence of a language barrier with the attending ART staff in symptomatic patients, since among clinicians (but not among nurses) were expatriates who did not speak the local language (table 1). Of symptomatic patients 46 (66%) said they had reported their complaints to the attending ART staff. Among symptomatic patients, age, gender, education level, duration of ART and WHO clinical stage at the start of ART were not associated with reporting symptoms to attending ART staff. As expected, patients who had reported their symptoms were more frequently attended to by clinicians instead of nurses, compared to those who had not reported symptoms (table 2). Patients with at least one severe symptom reported these with borderline significantly higher frequency than those who only had mild or moderate complaints.

In the electronic monitoring system, ART staff had only recorded 5 (4%) side effects, from 4 (5%) symptomatic patients, of whom 2 had both lipodystrophy and peripheral neuropathy. None of the symptoms yellow eyes[2] and rash[7] was recorded. In the population of this survey, the prevalence of symptoms that indicate characteristic side effects of the standard first line regimen was 39% based on our interviews, while it was 2% in the electronic monitoring system.

## Discussion

We found that symptoms regarded as side-effects of the standard first-line regimen were very common in adult Malawian ART patients. It is likely that we underestimated the prevalence of side-effects since we did not take the use of effective symptomatic treatments (for instance for peripheral neuropathy) into consideration. Only a small fraction of these symptoms were recorded as side-effects in the monitoring system and therefore most side-effects are not captured in local- and subsequently in national ART reports. A large number of patients (34%) do not mention their symptoms to attending ART staff and very few symptomatic patients (5%) are recorded as having toxicity by ART staff.

No factors that we considered were associated with being symptomatic and only severity of symptoms showed a borderline association with reporting to ART staff among symptomatic patients. Too few side effects were recorded for a meaningful analysis of factors associated with discrepancy between reporting and recording.

It is uncertain why patients do not report symptoms to ART staff. They may be given limited opportunity to present symptoms by ART staff or may find long clinic waiting times obstructive to discuss problems. ART staff may have too little time or see too little benefit in recording side-effects, for instance they may only record side-effects if they are actually planning to change treatment due to toxicity. It is less likely that symptoms were noted by ART staff but disregarded as toxicity, since 89% of symptomatic patients had characteristic symptoms that are well known by the experienced local ART staff as side-effects of stavudine-lamivudine-nevirapine.

A limitation of this survey is that we did not interview ART staff to confirm whether patients had actually mentioned symptoms to them, nor did we evaluate why symptoms were not recorded as side-effects if reported by patients. However, we felt it was crucial to avoid disclosing the nature of the survey to the ART staff. Further, this is a single centre survey and results may not be extrapolated to other settings. Given that ART reports from QECH indicate higher prevalence of side effects than national ART reports, it may be the case that under-recording is even higher in other clinics; alternatively the partly tertiary ART population in QECH may just have more toxicities.

## Conclusions

There was gross under-recording of side effects in the routine setting of a busy urban ART clinic. We suspect that pressure of work and insufficient perceived benefit of side effect recording are main causes. Local and national ART reports may not reflect the true toxicity of the standard first-line regimen.

## Acknowledgements

We thank the patients and staff of the ART clinic of QECH. JJvO was supported by an anonymous donor through the Centre for Operational Research, International Union against Tuberculosis and Lung Disease, Paris, France.

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