METHODOLOGY

The methodology is divided in two parts:

Part 1: Development of a Pharmacovigilance programme

Part 2: Testing of the developed programme

A. By performing retrospective analysis of adverse drug reactions in HIV/AIDS and TB co-infected patients on HAART (Highly Active Anti Retroviral Therapy)

B. By conducting intensive adverse drug reaction monitoring in Psychiatry

Part 1: Development of a Pharmacovigilance programme

Development of a Pharmacovigilance programme involves the following steps:

A. Risk Minimization

Risk is the probability of an adverse effect in an organism, system or (sub) population caused under specified circumstances by exposure to an agent. Risk minimization is to reduce the severity or frequency of known adverse reactions.

Steps involved in Risk Minimization include:

a. Training

b. Safe care delivery
a. Training

i. Preparation of documentary for Pharmacovigilance for Visceral Leishmaniasis in India, Nepal, Bangladesh

Training is an important part of development of a Pharmacovigilance programme. To implement this, a documentary for Pharmacovigilance for Visceral Leishmaniasis in India, Nepal, Bangladesh was developed in collaboration and with funding from the World Health Organization Tropical Diseases Research Program (WHO-TDR), Geneva, Switzerland.

Visceral Leishmaniasis (VL) or Kala-Azar is a life threatening disease that occurs due to the bite of a sandfly and presents with fever of long duration, splenomegaly, anemia and progressive weight loss. It affects men, women and children especially from poor communities, it is prevalent in 62 countries, and 50% cases occur in northern states of India, Terai region of Nepal and Bangladesh. Miltefosine is a new oral drug which can be given on an outpatient basis and has been found to be effective in more than 90% of VL cases. Miltefosine has risks, especially if not used as per guidelines. It produces diarrhea, vomiting, nephrotoxicity, hepatotoxicity, rise in liver enzymes, Stevens-Johnson syndrome. Although not observed in patients, in animal studies it has produced teratogenicity, eye toxicity and an effect on spermatogenesis. It has been tested in approximately 3000 patients till now and rare adverse effects may have not been noticed as yet. It is therefore essential to take precautions while using Miltefosine to avoid side effects and also be vigilant to avoid harm.
Therefore an audiovisual training module (DVD) was developed to give information on use of miltefosine in the treatment of Kala-Azar. The training module is in the local language, Hindi and consists of three parts.

Image 1: Cover page of the documentary and the training manual
First Part of DVD

The first part of the DVD consists of a doctor-patient interaction in which the physician explains details about Kala-Azar to the patient (Image 2), the instructions and precautions to be taken by the patient while on a regimen of miltefosine (Image 4), the immediate remedial measures to be taken in the event of an adverse drug reaction (Image 5&6). This part also shows how the patient should complete the “patient card” which can be used for checking the compliance to treatment, compliance to contraception and collecting information on adverse events (Image 7).

Image 2: Doctor consulting the patient in detail about the treatment regimen
Image 3: Current available miltefosine tablets at the PHCs in Bihar

Image 4: Doctor highlighting the importance of contraception while on miltefosine treatment
Image 5: Counseling of a patient who has suffered adverse drug reaction due to miltefosine

Image 6: Nurse demonstrating the procedure to make ORS (Oral Rehydrating Solution)
Image 7: Doctor explaining how to complete patient card

Image 8: Doctor handling over the packet of miltefosine to the patient only after the patient agrees to follow contraception, follow the treatment religiously and completes the patient card.
Second Part of DVD

The second part of the DVD consists of a training module for the physicians, health workers and the technical staff. This part was originally in English, but based on feedback received was later developed in Hindi with only the technical terminologies in English. In this training module, viewers are trained in all aspects of miltefosine regimens including the symptoms of Kala-Azar, details about the rk 39 dip stick test for the diagnosis of Kala-Azar, advantages of using miltefosine as a drug of choice for the treatment of Kala-Azar, contraindications to the use of miltefosine, the manner in which a physician should counsel a patient regarding the precautions to be taken while treating patients, especially female patients with miltefosine like the use of contraception, avoidance of breast feeding, compliance to treatment, dosage calculation for adults as well as children and regular follow up.

Third part of DVD

The third part of the DVD consists of detailed information about the documentation of adverse events, how an adverse event should be reported, and the importance of reporting these adverse events and how to avoid the adverse drug reactions. This part also explains how to complete the OPD card developed for the Leishmaniasis elimination programme.

The patient information video (the first part) is of 16 mins duration and the training module for the physicians and healthcare workers (the latter two parts) is of 32 mins durations. Patients viewed only the first part of the video whereas physicians and health workers viewed all three parts of the presentation.
Filming and Production of the documentary

The filming and production of the entire video was conducted at Mumbai, Maharashtra.

ii. Testing of the documentary in PHCs of Bihar

The DVD with the training module was field tested at the Rajendra Memorial Research Institute of Medical Sciences (RMRI), Patna and Public Health Centers (PHCs) in 3 districts of Bihar (Saran, Muzaffarpur and East Champaran). The PHCs were chosen because miltefosine was already being administered at these PHCs to patients, under the National Program for Elimination of Kala-Azar. The video was shown to physicians, healthcare workers and patients using a laptop.

In order to evaluate the impact of the training module on the understanding of the health workers and patients about the appropriate use of miltefosine, a survey questionnaire was developed. The questionnaire for physicians was in English and consisted of 17 multiple choice questions with possibly more than one answer being correct. The questions pertained to presenting symptoms of Kala-Azar, the adverse events noted during animal studies, duration of Kala-Azar treatment and commonly occurring Adverse Drug Reactions (ADRs) to miltefosine. Each correct answer was allocated one point. The total correct answers to the questions were 35, and so the physicians could score a maximum of 35 points.

For the patients and the health workers the questionnaire consisted of 14 multiple-choice questions that tested basic knowledge such as the name of the vector that causes Kala-Azar, the symptoms of Kala-Azar, the duration of treatment and regimen with
miltefosine, methods and duration of contraception required and protocols to be followed in the event of ADRs. Each question had one correct answer and each correct answer carried 1 point; so, the patients and health workers were marked out of 14.

This questionnaire (Appendix 1 and Appendix 2) was circulated twice, once before and once after viewing the video and the responses were correspondingly recorded. The physicians filled out the questionnaires themselves, while for the patients; the questionnaire was administered by me and staff of RMRI. Verbal consent was obtained from the patients before asking these questions. To avoid bias, physicians of RMRI assisted in questioning patients.

b. Safe care delivery (instructions for safe use of drugs)

It includes use of appropriate formulation (pediatric formulation incase of children), provision for dispensing information, use of checklist in outpatients, provision for a patient held treatment card.

For ensuring safe care delivery Kala- Azar 2 page OPD card, Kala-Azar 4 page OPD card and Patient card was developed to ensure accurate dose calculation, proper dispensing of miltefosine, and checklist before starting treatment.

i. Preparation of Kala-Azar 2 page OPD card

Kala-Azar 2 page OPD card was developed to capture information on demographic details, age, sex, height and weight, laboratory tests, clinical features, rk39 dip stick test, treatment given to the patient if he/she were an old case of Kala-Azar, past/concurrent history, medications taken in the last two weeks/ongoing medications, results of urine
pregnancy tests at first visit, after 2 weeks, completion of treatment and subsequently after 3 months of completion of treatment, counseling given to the patient on different precautions to be taken while on miltefosine treatment, choice of primary and secondary contraception, dosage regimen for adults as well as children above 2 years of age, miltefosine dispensed at every visit which will help to check for compliance, treatment outcomes, and follow up results at 3 and 6 months after completion of treatment. The OPD card is filled by ticking in the appropriate boxes. For visit notes the OPD card provides enough space to record as free text. This two page OPD card was developed for regular use in the OPD/PHC where not much time is available for the physician to complete a detailed four page OPD card. But where a dedicated person is available for pharmacovigilance of miltefosine, the Kala-Azar 4 page OPD card would be used.

ii. Preparation of Kala-Azar 4 page OPD card

In view of capturing complete information related to adverse events the Kala-Azar 4 page OPD card was developed. This card is useful for capturing the severity, likely cause and outcome of the adverse event. Here, one entire page is provided for capturing the adverse events in the form. Commonly occurring adverse events were coded from A-M in the AE/ADR code table for eg. Nausea and vomiting was coded as “A” and so on. If the adverse event is not from the table and it is new then codes from N-R were given, the physician will assign the code to the adverse event .Physicians will also decide the seriousness, severity, likely causes, actions taken, treatment of reaction and outcome of reaction of the adverse event as per WHO scale and enter the same on the OPD card. This will help in capturing of information required for assessment of the AE.
iii. Preparation of Patient card

To capture the compliance to treatment, compliance to contraception by female patients (in case of OC pills) and for reporting of any adverse events during treatment by patients a “patient card” was developed in Hindi which is the local language of Bihar. The patient card consists of the date and results of the urine pregnancy tests, choice and date of contraception used and daily record of compliance to treatment. After taking miltefosine the patients are supposed to tick against the date in the patient card. Also space is provided for the patients to write down any adverse events that they experience during treatment in this card.

B. Risk Assessment

Risk assessment is the process of identifying, estimating and evaluating the nature and severity of risks associated with a product throughout its lifecycle. Various methods are used for assessment of risks which involve active surveillance and passive surveillance. Active surveillance involves cohort event monitoring, intensive monitoring etc. Passive surveillance involves spontaneous reporting and focused reporting. Spontaneous reporting method was selected for the study.

Training was imparted to me for causality assessment and data entry into Vigiflow, a web-based Individual Case Safety Report (ICSR) management system that is specially designed for use by national centers in the WHO Programme for International Drug Monitoring. It can also be used by pharmaceutical companies or clinical research organizations for monitoring of their ICSR.
VigiFlow is based on and compliant with the ICH E2B standard and is a trademark of the UMC and maintained by the UMC in Uppsala, Sweden. This training was imparted in two stages:

1. The importance of WHO Programme for International Drug Monitoring was stressed upon and the concept of Individual Case Safety Report (ICSR), assessment and subsequent submission to WHO through Vigiflow was explained in detail. This was followed by a practical demonstration of causality assessment and coding as per WHO-ART, MedDRA coding dictionaries and the process of data entry into Vigiflow.

2. 100 spontaneous reports were randomly selected from the archives of spontaneous reports maintained at the Department of Clinical Pharmacology, KEM hospital which is the south west zonal center of the National Pharmacovigilance Programme. These reports were analyzed for quality which includes completeness and consistency of data. The reports fulfilling the basic criteria, which is identifiable adverse event, identifiable drug, identifiable patient and identifiable reporter were selected for assessment and data entry. All adverse drug reactions and related suspected medications of these forms were coded as per WHO-ART, MedDRA coding dictionaries, indications were coded as per ICD-10. This data was entered into the Vigiflow database as per knowledge gained in the first stage of the training. The data from these forms was reviewed by officials from WHO and feedback was provided on the same.
Certification from WHO

To obtain certification from WHO’s Uppsala monitoring centre, Sweden for “Data entry into Vigiflow”, the WHO officials provided 4 spontaneous CIOMS (Council for International Organization of Medical Sciences) case report forms from the country Tanzania. These case reports were of different types namely hypersensitivity case report, congenital anomaly case report, literature case report and fatal case report. These case reports were assessed for causality and were further entered into the Vigiflow database for assessment by WHO officials.

C. Analysis of Pharmacovigilance data

Spontaneous reports from 4 African countries namely Tanzania, Zambia, Sierra Leone and Ghana were received from their respective National Regulatory Authority/Pharmacovigilance centre. These reports were assessed for quality of data. The case reports having complete information with respect to identifiable adverse event, identifiable drug, identifiable patient and identifiable reporter were assessed for causality as per WHO scale and entered into the Vigiflow database online. Drugs, diseases, indications, adverse events reported were coded as per WHO-ART, MedDRA, ICD-10 dictionaries. Evaluation of the expectedness of ADRs was done (i.e. whether the nature, severity and specificity of the reported adverse reaction were consistent with the adverse reaction terms mentioned in the standard text of Martindale: The Complete Drug Reference & Physician’s Desk Reference). A causality assessment report based on WHO causality assessment grading was prepared and a brief medical narrative of the ADR
cases was prepared. Subsequently, a Vigiflow report was generated for each ADR case. Finally, line listings and a consolidated summary of ADR assessment were generated and communicated to respective countries. These reports were further entered into the individual countries’ national databases.

Part 2: Testing of the developed programme

Testing of the developed Pharmacovigilance programme was carried out in 2 parts:

A. By performing retrospective analysis of adverse drug reactions in HIV/AIDS and TB co infected patients on HAART (Highly Active Anti Retroviral Therapy)

A retrospective study was carried out to analyze the ADRs reported in HIV/AIDS and HIV/ TB co infected patients on HAART (Highly Active Anti Retroviral Therapy)

i. Study design

A retrospective study was conducted at the King Edward VII Memorial (KEM) Hospital an 1800 bedded tertiary referral center in Mumbai (Bombay), India. The data which is routinely collected at each consultation and maintained at the ART centre was studied. The study protocol was approved by the institutional ethics committee.

ii. Setting

Antiretroviral centre was established at KEM Hospital in November 2005 at which free ART treatment was offered to patients either at WHO stages I,II or III with CD4 count ≤200 cells/µL or at WHO stage IV irrespective of CD4 count as per WHO recommendations and national HAART protocol. Most patients were initiated on fixed-
dose combination of stavudine-lamivudine-nevirapine but in case of intolerance or contraindications, other alternative combinations such as d4T+3TC+EFV, AZT+3TC+NVP and AZT+3TC+EFV were prescribed.

ART centre maintains each patient record form on which data is routinely entered at each consultation visit. The content of this record form includes demographic details of the patient, possible route of infection, family history, earlier treatment details, current medication, laboratory results and information about adverse event. Information of adverse event includes name of adverse event, its starting date and whether treatment was changed due to adverse event.

**iii. Study population**

The study population included primarily HIV/AIDS and HIV/TB co infected adults who had been taking anti retroviral treatment at ART centre since 15 November 2005. The patient record forms from 15 Nov 2005 to 31 Dec 2007 were reviewed.

**iv. Data Collection**

The data was collected on to the case record form (CRF) (Appendix 3) and was also entered onto adverse drug event reporting form of Central Drugs Standard Control Organization (CDSCO), Delhi (Appendix 11). Demographic details of the patients, name of ART combination prescribed, its date of initiation, name of adverse reaction mentioned, if rechallenge performed and its outcome was captured.
v. Data Assessment

Causality assessments of adverse drug reactions were done as per Naranjo causality assessment scale. ADRs were classified as Definite, Probable, Possible and Doubtful. The extent of severity and preventability of all the cases was assessed by Hartwig and Seigel scale and Schumock & Thornton scale respectively.

vi. Statistical analysis

Descriptive statistics were performed by using Microsoft Excel. Frequency of ADRs and median time of exposure of ART to develop ADRs were calculated. Odds ratio with 95% Confidence Interval (CI) was calculated for ADRs in patients with HIV and patients with HIV/TB co infection on HAART.

B. To test the developed programme by conducting intensive adverse drug reaction monitoring in Psychiatry

A prospective observational study was carried out at the Psychiatry OPD (Out Patient Department) of King Edward VII Memorial (KEM) Hospital.

i. Study design

A prospective observational study was conducted for one year duration from November 2009 to November 2010 at the Psychiatry OPD (Out Patient Department) of King Edward VII Memorial (KEM) Hospital. The study was initiated after approval from the institutional ethics committee.
ii. Settings

Psychiatry OPD is conducted 6 days a week (Monday to Saturday) in the morning. The OPD was attended regularly and information of patients with ADRs was collected.

iii. Study population

The study population included patient attending the psychiatric OPD during the time period from November 2009 to November 2010. Being a prospective observational study, Patients in the age group of 18-65 yrs and receiving antipsychotics, antidepressants, antimanics and antiepileptics were included in this study. However treatment naïve patients were excluded from the study, as adverse drug reactions in this population is not seen.

iv. Data Collection

Patients with suspected adverse drug reactions were referred by the treating physician to me. Informed consent was administered to the patient/ legal guardian. After which a unique patient identification number was given to the patient for ease of follow up. The patient was interviewed and data was captured onto the case record form (Appendix 6) and was also captured onto the CDSCO Adverse drug reaction reporting form (Appendix 11). Information regarding demographic details, current medication, health status, previous history and adverse events experienced were recorded.
v. Data Assessment

Causality assessments of adverse drug reactions were carried out as per Naranjo causality assessment scale. A variety of scales, algorithms, and nomograms have been published to improve the accuracy and decrease variability among assessors. Despite these efforts, the precision and accuracy of assessing the relationship between drug administration and an adverse drug event remain uncertain. The Naranjo adverse drug reaction probability nomogram was chosen as assessment instrument because it is simple to use, is clinically appropriate, and is at least as precise and accurate as other causality methods. In addition, the Naranjo nomogram has been widely used and cited in the biomedical literature.

Causality was classified as Definite, Probable, Possible and Doubtful. Severity of adverse drug reactions were assessed by Hartwig and Seigel scale and preventability was assessed by and Schumock & Thornton scale. Seriousness was assessed as per WHO criteria for seriousness.

vi. Statistical analysis

Descriptive statistics were performed by using Microsoft Excel.
vii. Flow chart of the study

The study was initiated after the Ethics Committee approval

Patients attending the Psychiatry OPD were selected for the study

Patients were examined by the Physicians

Patients having confirmed AEs were directed and interviewed after their written informed consent

AEs were entered onto the case record form (CRF)

AEs were also entered into the CDSCO (Central Drug Standard Control Organization) form

AEs were assessed for Causality (Naranjo scale), Seriousness (as per the WHO criteria for Seriousness), Preventability (Schumock & Thornton) and Severity (Hartwig & Seigel scale)

Data analysis

Results