LITERATURE REVIEW

Literature review is divided into four parts

3.1: Importance of ADRs, classification and current methods for pharmacovigilance, the National Pharmacovigilance program, overview of the Pharmacovigilance system for ADR monitoring, importance of risk management which includes risk assessment and risk minimization

3.2: Highly Active Anti Retroviral Therapy (HAART)

3.3: Psychotropic drug therapy

3.4: Kala-Azar and the use of miltefosine

3.1 Overview of Pharmacovigilance Program

3.1.1 What is an Adverse Event (AE)?

‘Any untoward medical occurrence that may appear during treatment with the pharmaceutical product but which does not necessarily have a causal relationship with the treatment’.

An adverse event (AE) can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptoms or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
3.1.2 What is Adverse Drug Reaction (ADR)?

'A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological functions'.

Eg: The drug Reserpine which is widely used to treat hypertension is sometimes know to cause depression in patients. This is a serious and unintended effect of the drug and thus can be classified as an Adverse Drug Reaction of Reserpine. Similarly Haemolytic Anaemia is reported with use of methyldopa, cholestatic hepatitis with erythromycin estolate, hepatocellular hepatitis with fluothane etc.

3.1.3 What is an Unexpected Adverse Drug Reaction (ADR)?

An ADR whose nature, intensity or incidence falls outside the information provided in

- the Investigator’s Brochure
- the Package Insert or Product Monograph of a marketed drug

Eg: Thalidomide was initially marketed as an anti emetic but numerous unexpected cases of Congenital malformations were reported, the information on which was previously unavailable. This was an unexpected ADR of Thalidomide.

3.1.4 Importance of Adverse Drug Reactions (ADR)

Studies have shown that ADRs account for about 2%-6% of all hospital admissions. A recent meta analyses has suggested that ADRs are the fourth and sixth leading cause of death in United States. Surveys conducted recently have also shown that adverse drug events are associated with an increased length of stay in hospitals there by leading to an increased cost of therapy per patient.
The various direct and indirect effects of adverse drug reactions are:

- Adverse effects on patient quality of life
- Admission to hospital or attendance in primary health centre
- Prolongation of inpatient hospitalization
- Increase in cost of patient care
- Loss of confidence in the treating doctor by the patient
- Death/ permanent disability/ congenital anomaly or birth defects due to adverse reactions

3.1.5 Classification of Adverse Drug Reactions:

There are seven different ways for classification of adverse drug reactions.

3.1.5.1 Pharmacological classification

**Type A (Augmented):** It is due to an extension of the active pharmacologic properties of the drug. They are also called predictable or anticipated events. These are the commonest type (up to 70%), are dose dependant hence severity increases with dose. These ADRs are preventable in most part by slow reduction of doses.

There are two subclasses:-

- Exaggerated Desired Effect
- Undesired Effects

Eg. Hypoglycemia with sulfonylureas

Sulfonylureas are used for the management of Diabetes Mellitus. They sometimes may cause hypoglycemia as a result of excesses in insulin production and release. This typically occurs if the dose is too high, and the patient is fasting.
**Type B (Bizzare):** These are called pharmacologically unexpected, unpredictable, or idiosyncratic adverse reactions. They are unrelated to the dose of the drug.

There are two subclasses:

- Immunologic
- Idiosyncratic

Eg. Anaphylaxis with penicillin

Anaphylaxis is a sudden, potentially life-threatening allergic reaction. Symptoms include those of an allergic reaction, as well as very low blood pressure, difficulty in breathing, abdominal pain, swelling of the throat or tongue, and/or diarrhea or vomiting. It can be caused by the administration of Penicillin, which is commonly used to treat bacterial infections and illnesses. Causes could be that a person could be allergic to Penicillin.

**Table 1: Characteristics of Type A and Type B adverse reactions**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacologically predictable</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dose dependant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Frequency</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Incidence</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Mortality</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Treatment</td>
<td>Adjust dose</td>
<td>Stop the drug</td>
</tr>
</tbody>
</table>

**Type C (Chronic effect after prolonged use):** These types of ADRs occur as a result of chronic effect due to prolonged use of the drug. These ADRs may be irreversible, unexpected, and unpredictable.
Eg: Colonic dysfunction due to laxatives. Overuse of laxatives over a period of time causes colonic dysfunction (constipation or diarrhea).

**Type D (Delayed):** These types of ADRs are characterized by delayed occurrence after many years of treatment or in the children of treated patients.

Eg. Craniofacial malformations in infants whose mothers have taken isotretinoin.

**Type E (End of Treatment):** These types of ADRs are usually characterized by withdrawal reactions.

Eg: Seizure on alcohol or benzodiazepine withdrawal.

Benzodiazepine withdrawal in severe cases provokes life-threatening withdrawal symptoms, such as seizures.

**Type F (Failure of therapy):** This type of ADRs result from ineffective treatment may also be called as lack of efficacy.

Eg: accelerated hypertension because of inefficient control.

3.1.5.2 **Classification based on Causality (WHO-UMC Classification)**

WHO-UMC classifies adverse drug reactions into following categories:

**Certain**

A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically, using a satisfactory rechallenge procedure if necessary.
Probable
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely
A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/ Unclassified
A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessable/ Unclassifiable
A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified
3.1.5.3 Naranjo’s Algorithm for Causality Assessment\textsuperscript{28}:

There are nine questions, each question has scores assigned for the answers Yes, No and Don’t Know. After answering all the questions the scores are totaled and the final score is used for interpreting the causality of the adverse event.

1. Are there previous conclusive reports on this reaction?
   
   \textit{Yes} (+1) \textit{No} (0) \textit{Do not know or not done} (0)

2. Did the adverse event appear after the suspected drug was given?
   
   \textit{Yes} (+2) \textit{No} (-1) \textit{Do not know or not done} (0)

3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?
   
   \textit{Yes} (+1) \textit{No} (0) \textit{Do not know or not done} (0)

4. Did the adverse reaction appear when the drug was readministered?
   
   \textit{Yes} (+2) \textit{No} (-1) \textit{Do not know or not done} (0)

5. Are there alternative causes that could have caused the reaction?
   
   \textit{Yes} (-1) \textit{No} (+2) \textit{Do not know or not done} (0)

6. Did the reaction reappear when a placebo was given?
   
   \textit{Yes} (-1) \textit{No} (+1) \textit{Do not know or not done} (0)

7. Was the drug detected in any body fluid in toxic concentrations?
   
   \textit{Yes} (+1) \textit{No} (0) \textit{Do not know or not done} (0)

8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?
   
   \textit{Yes} (+1) \textit{No} (0) \textit{Do not know or not done} (0)

9. Did the patient have a similar reaction to the same or similar drugs in any previous
exposure?

Yes (+1) No (0) Do not know or not done (0)

10. Was the adverse event confirmed by any objective evidence?

Yes (+1) No (0) Do not know or not done (0)

**Scoring**

> 9 = definite ADR

5-8 = probable ADR

1-4 = possible ADR

0 = doubtful ADR

**3.1.5.4 Severity Classification**

Adverse drug reactions are classified based on severity into three categories:

- **Mild / Minor**: No antidote, therapy or prolongation of hospitalization is required.

- **Moderate**: requires change in drug therapy, specific treatment, or an increase in hospitalization at least by a day.

- **Severe**: potentially life threatening, causing permanent damage or requiring intensive medical care.
3.1.5.4 Hartwig And Siegel scale for Severity Assessment

Table 2: Hartwig And Siegel scale for Severity Assessment

<table>
<thead>
<tr>
<th>Definition</th>
<th>Severity Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required no change in treatment with suspected drug</td>
<td>1</td>
</tr>
<tr>
<td>Drug dosing or frequency changed ,without antidote or treatment for exhibited symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Required treatment or drug administration discontinued</td>
<td>3</td>
</tr>
<tr>
<td>Resulted in patient transfer to higher level of care</td>
<td>4</td>
</tr>
<tr>
<td>Caused permanent harm to the patient or significant hemodynamic instability</td>
<td>5</td>
</tr>
<tr>
<td>Directly or indirectly resulted in patient’s death</td>
<td>6</td>
</tr>
</tbody>
</table>

Severity Levels

Level 1 & 2 – Mild

Level 1 & 2 – Moderate

Level 1 & 2 – Severe

3.1.5.6 Seriousness Classification

Any untoward medical occurrence that at any dose causes the following is known as a serious adverse event;

- Results in Death
- Is life threatening
- Requires inpatient hospitalization/prolongation of existing hospitalization
- Results in persistent of significant disability or incapacity is a serious adverse event
• Results in congenital anomaly
• Other medically important conditions

3.1.5.7 Preventability assessment by Schumock & Thornton scale\textsuperscript{32}

1. Was the drug involved in the ADR not considered appropriate for the patient’s clinical condition?

2. Were the dose, route and frequency of administration not appropriate for the patient’s weight and disease status?

3. Was required therapeutic drug monitoring or necessary laboratory test not performed?

4. Was there history of allergy or previous reaction to the drug?

5. Was a drug interaction involved in the reaction?

6. Was a toxic serum drug concentration documented?

7. Was poor compliance involved in the reaction?

If answer to any question is “yes”, the ADR is classified as preventable

3.1.6 Current methods of Pharmacovigilance

As per the ICHE2E\textsuperscript{33} guidelines Pharmacovigilance methods can be categorized as:

1. Passive surveillance
   a. Spontaneous reporting
   b. Case series

2. Stimulated reporting

3. Active surveillance
a. Sentinel sites
b. Drug event monitoring
c. Registries

4. Comparative observational studies
   a. Cross sectional study
   b. Case control study
   c. Cohort study

5. Targeted clinical investigations

6. Descriptive studies
   a. Natural history of disease
   b. Drug utilization study

3.1.6.1 Passive Surveillance

a. Spontaneous reports:

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g. WHO regional centers, Poison control centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme[^34]. This type of report is voluntary in nature (voluntary reporting) i.e. it may be initiated by the healthcare professionals or consumers as and when they become suspicious of any adverse reaction by any medication.

Doctors of other healthcare professionals (e.g. pharmacists, nurses) are provided with a form by the concerned regulatory authority or the organization working under the aegis of the government regulatory authorities. In India the form used for spontaneous
reporting is known as “Suspected Adverse Reaction Reporting Form” generated by CDSCO (Central Drug Standard Control Organization) working under the aegis of the Directorate General of Health Services (DGHS), Government of India.

- Spontaneous reports play a major role in the identification of safety signals once a drug is marketed.
- It provides the highest volume of information at the lowest maintenance cost
- Requires low set up and running costs
- Allows perpetual monitoring for all drugs after marketing
- It may generate rapid alerts and stimulate follow up
- Is not limited to monitoring of specific patient groups
- Has wide coverage

However there are some weaknesses to spontaneous reporting, they are

- Under reporting
- Number of patients exposed is unknown
- Information is often incomplete and there may be reporting bias
- Quality of reporting information vary greatly
- Dependant on reporters to identify an event as a reaction to the drug
- Medical professionals do not see this as a priority
- If symptoms are not serious they may not get noticed or if the symptoms are serious they may not be recognized as an effect to the drug.
3.1.6.2 Case series

Case report describes the particular outcome or experience of a person who has been exposed to a drug. These reports are useful for generating hypotheses about the effects of the drug, may lead to further studies to test these hypotheses. A case series, involves reports on two or more people with common exposure to a drug, or a common outcome. Series of case reports can provide evidences between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome\textsuperscript{33}.

3.1.6.3 Stimulated Reporting

Stimulated reports are those that may be motivated or induced and can occur in certain situations, such as notifications by a Health Care Professional Communication (HCPC), public advisory, literature reports, publications in the press. These reports are considered unsolicited in nature and as form of spontaneous reporting. Data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated\textsuperscript{33}.

3.1.6.4 Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active
surveillance system than through a passive reporting system. The various methods to get the comprehensive data through active surveillance are mentioned below:

**a. Sentinel sites**

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites can provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, information on the use of a drug, such as the potential for abuse, can be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs.

Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, hemodialysis centers, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

**b. Drug event monitoring**

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each
prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire. Limitations of drug event monitoring include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

c. Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug) registry. Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition.

Exposure (drug) registries address populations exposed to medicinal products of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.
3.1.6.4 Comparative Observational Studies

Traditional epidemiologic methods are key components in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).  

a. Cross-sectional study (survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured.
b. Case-control study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time.

Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunction, which might modify the relationship between the drug exposure and the adverse event.\textsuperscript{33}

c. Cohort study

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort
studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time\textsuperscript{33}.

3.1.6.5 Targeted Clinical Investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolize drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event,
alarge simplified trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. In this type of trial, though, the event of interest will be focused to ensure a convenient and practical study. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial.

3.1.6.6 Descriptive Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

a. Natural history of disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest can be used to assist in putting spontaneous reports into perspective. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.
b. **Drug utilization study**

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.

DUS can be used to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice.

These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies may include a lack of clinical outcome data or information of the indication for use of a product.

### 3.1.7 Signal Detection in Pharmacovigilance

A signal can be defined as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. A signal can arise from post marketing data and other sources such as preclinical data. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of information. But a single
well documented case report can be viewed as a signal particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of the drug. When different factors independently report the same unknown and unexpected experiences with a drug, it can be an important signal. Thus signal indicates the need for further investigation which may or may not lead to the conclusion that the product caused the event.

**Sources of signal**

- Observation in individual patients
- Observations in populations
- Clinical or preclinical experimental findings
- Medical information published in medical journals or observed during clinical studies may generate signals for adverse effects of drugs

Safety signal refers to a concern about an apparent excess of adverse events compared to what could be expected. It can be preclinical findings or experience with other products, even in the absence of case reports in patients. After identifying a safety signal, it should be further assessed to determine whether it represents a potential safety risk which warrants further studies. Data of a signal may be Qualitative (clinical) or Quantitative (epidemiological).

Safety signals may come either prior to a product’s marketing approval or after a product is marketed. Plans for pharmacovigilance will depend on

- Nature of the signal
- Whether it is common or rare
• Nature of population (s)
• Whether the product is prescribed to broad range of patients or selected population only
• Whether the product is dispensed at all pharmacies or via restricted distribution only.

Development of pharmacovigilance plans is useful at the time of product launch or when a safety signal is identified. If a product is without safety signals (pre and post marketing and risk populations are adequately studied) then the pharmacovigilance simply proposed as routine spontaneous reporting. Periodic Safety Update Reports (PSURs) can also identify new safety signals and are effective means of risk communication to the regulatory agencies, means of determining change in the risk benefit ratio and indicator for the need of risk management programs35.

3.1.8 Risk management in Pharmacovigilance

It is recognized that at the time of authorization, information on the safety of a medicinal product is relatively limited. This is due to many factors including the small numbers of subjects in clinical trials, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes. A medicinal product is authorized on the basis that in the specified indication(s), at the time of authorization, the benefit-risk is judged positive for the target population. However, not all actual or potential risks will have been identified when an initial authorization is sought. In addition, there may be subsets of patients for whom the risk is greater than that for the target population as a whole. Therefore risk
management in Pharmacovigilance becomes crucial. A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of interventions. It involves risk assessment and risk minimization.\(^{36}\)

Risk assessment is a process of identifying, estimating and evaluating the nature and severity of the risks associated with the product throughout its life cycle.\(^{37}\) Although medical products are required to be safe, safety does not mean zero risk. A safe product is the one that has reasonable risks, given the magnitude of benefit involved and alternatives.

Pharmacovigilance and risk management activities that might be included in a Risk Management Plan fall into two categories:

a. Routine activities—which would generally be conducted for any medicine at the same stage of development where no special safety concerns have arisen and additional activities designed to address identified safety concerns. Routine pharmacovigilance would include the safety evaluations incorporated in clinical trials and the monitoring and reporting of spontaneous adverse events post approval. Routine risk management activities would include ensuring that suitable warnings are included with all product information and careful labeling/packaging of the medicine.

b. In a Risk Management Plan, the action plan might include calling for additional pharmacovigilance in the form of.\(^{38}\)
• Active surveillance (eg, medical records reviews, patient or physician interviews, prescription event monitoring, data from disease or drug exposure registries).

• Epidemiology studies (retrospective or prospective).

• Further clinical studies (specific safety studies, larger studies over longer periods).

• Drug utilization studies (which describe how a drug is marketed, prescribed, and used in a specified population—often stratified by age, gender, concomitant medications, etc—and how these factors influence clinical, social, and economic outcomes).

Additional risk minimization activities include:

• Additional educational material about the medicine and its use (patient information brochures, visual aids, physician prescribing guides/checklists, pharmacist dispensing guides/checklists, health care provider letters).

• Training programs (patient- or physician-oriented).

• Restricted use of the medicine (eg, for use/dispensing only in hospital, or where specific equipment [eg, resuscitation equipment] is available; availability only in limited unit sizes.

Therefore risk management is an interactive process of:

• Assessing product’s benefit-risk balance

• Developing and implementing tools to minimize risk

• Evaluating tool effectiveness, reassessing the benefit-risk balance
• Making appropriate adjustments to the risk minimization tool to further improve the benefit-risk balance\textsuperscript{40}

### 3.1.9 The National Pharmacovigilance Program\textsuperscript{41}

The Central Drugs Standard Control Organization (CDSCO) has initiated a well structured and highly participative National Pharmacovigilance Programme. It was officially inaugurated by the Honorable Health Minister Dr.Anbumani Ramadoss on 23 November, 2004 at New Delhi.

The specific aims of the Pharmacovigilance Programme are to:

- Contribute to the regulatory assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective\textsuperscript{(including cost effective)} use
- Improve patient care and safety in relation to use of medicines and all medical and paramedical interventions
- Improve public health and safety in relation to use of medicines
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public

The Programme aims to foster the culture of ADE notification in its first year of operation and subsequently aims to generate broad based ADR data on the Indian population and share the information with global health-care community through WHO-UMC\textsuperscript{41}. 

\textsuperscript{40}Text from the original document.

\textsuperscript{41}Text from the original document.
Under the program 26 peripheral centers, 5 Regional Centers and 2 Zonal Centers were established. The Peripheral centers will record the Adverse Events (AE) and send to the Regional Centers. They in turn collate and scrutinize the data received from the Peripheral Centers and submit to the Zonal Centers. The Zonal Centers will analyze the data and submit consolidated information to the National Pharmacovigilance Centre. The Zonal Centre will also provide training, general support and coordinate the functioning of the Regional Centers.

Figure 1: Flow of information

The National Pharmacovigilance Advisory Committee (NPAC) oversee the performance of various Zonal, Regional and Peripheral Pharmacovigilance centers as well as recommend possible regulatory measures based on the data received from various centers. It also oversees data collection and assessment, interpretation of data as well as publication of ADR monitoring data. The Committee also periodically evaluates their protocol compliance levels to ensure that the data received is homogenous and can be
scientifically pooled for informed regulatory decisions. Wherever necessary, NPAC also seeks the opinion of experts in various specializations⁴¹.

**Figure 2: National Pharmacovigilance programme structure**

3.1.10 **WHO Programme for International Drug Monitoring**⁴²

Since 1978, UMC has managed primary aspects of the expanding worldwide pharmacovigilance network of the now more than 130 countries, known as the WHO Programme of International Drug Monitoring.

As of July 2011, 106 countries have joined the WHO Drug Monitoring Programme, and in addition 34 'associate members' are waiting for full membership while compatibility between the national and international reporting formats is being established.
In accordance with an agreement between WHO and the Government of Sweden, the WHO Headquarters is responsible for policy issues, while the operational responsibility rests with the Uppsala Monitoring Centre (UMC).

Functions of the WHO Programme for International Drug Monitoring include:

- Identification and analysis of new adverse reaction signals from the case report information submitted to the National Centres, and sent from them to the WHO ICSR database. A data-mining approach (BCPNN) is used at the UMC to support the clinical analysis made by a panel of signal reviewers.
- Provision of the WHO database as a reference source for signal strengthening and ad hoc investigations. Web-based search facilities and customized services are available.
- Information exchange between WHO, UMC and National Centres, mainly through 'Vigimed', an internet based information exchange system.
- Publication of periodical newsletters, (WHO Pharmaceuticals Newsletter and Uppsala Reports), guidelines and books in the pharmacovigilance and risk management area.
- Supply of tools for management of clinical information including individual case safety reports. The main products are the WHO Drug Dictionary and the WHO Adverse Reaction Terminology.
- Provision of training and consultancy support to National Centres and countries establishing pharmacovigilance systems.
- Computer software for case report management designed to suit the needs of National Centres (VigiFlow)
- Annual meetings for representatives of National Centres at which current pharmacovigilance issues and the development of the programme are discussed.
Methodological research for the development of pharmacovigilance as a science.

3.1.11 Vigibase

Vigibase is the name of the WHO global ICSR database; it consists of reports of adverse reactions received from member countries since 1968. VigiBase is updated with incoming ICSRs on a continuous basis. National centers are recommended to send reports at least quarterly; most national centers adhere to these guidelines.

The VigiBase data resource is the largest and most comprehensive in the world, and it is developed and maintained by the Uppsala Monitoring Centre (UMC) on behalf of the World Health Organization. VigiBase is a computerized pharmacovigilance system, in which information is recorded in a structured, hierarchical form to allow for easy and flexible retrieval and analysis of the data. The case reports in the WHO database do not identify the patient or reporter. Its purpose is to provide the evidence from which potential medicine safety hazards may be detected. The VigiBase database system includes linked databases containing medical and drug classifications: WHO-ART/MedDRA, WHO ICD, and WHO-DD. These classifications enable structured data entry, retrieval, and analysis at different levels of precision and aggregation.

3.1.12 Vigiflow

VigiFlow is a web-based Individual Case Safety Report (ICSR) management system that is specially designed for use by national centres 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.

**a. Input**

ICSR data can be manually entered into VigiFlow with support from the latest versions of terminologies such as the WHO Drug Dictionary and WHO-ART or MedDRA. Some fields are mandatory, and this, together with built-in error checks, helps users to add data correctly. It is also possible to import ICSR data as XML files in the E2B format. If a country has regional pharmacovigilance centres, the manual entry of ICSRs can be done at this level.

**b. Handling of ICSRs**

It is easy to communicate within VigiFlow by adding a digital ‘post-it’ note to the ICSR. This note will stay with the report when it is sent from a regional centre to the national centre or while different people at the national centre work on the report. Once a report is complete and committed the first version of the ICSR is considered to be finalized. It is easy to retrieve reports to amend the contents or add follow-up information. An audit trail on each report will keep copies of earlier versions and show which user added new information.

**c. Analysis of ICSRs**

A search and statistics module is part of VigiFlow; both line listings and statistical tools are among the profiles available. The results can be exported in different output formats, either as PDF files or in spreadsheet format compatible with Microsoft Excel.
d. Communication with External Organizations

ICSR data can be sent to external contacts such as companies or other regulatory agencies either as PDF files (as computer files or hardcopy printouts) or in E2B formatted XML files. The submission manager in VigiFlow will keep track of which ICSRs should be sent to an external contact and which have already been sent. All imported E2B files are tracked.

ICSRs will automatically be flagged for being copied to VigiBase, the WHO Global ICSR database when they are committed; however, national centres can easily remove this and thereby keep a specific report private.43

e. Technical Information

Since VigiFlow works over the Internet, no local installations, back-ups or maintenance are necessary. The only requirements are a web browser, preferably Mozilla Firefox or Internet Explorer and an Internet connection. The Internet access is encrypted and any information stored in VigiFlow is only accessible by users within the same country/organisation identified by their individual user name and password.43

f. Free of Charge Version

The UMC charges a nominal license fee for full access to the functionality described above. However, a version of VigiFlow with limited access is available free of charge to member countries of the WHO Programme. The functionality not available includes the E2B import and export and the search and statistics module. The free of charge version is not a complete management system and is primarily meant to be used for sending ICSRs to the UMC.43
3.1.13 Dictionaries used for coding\textsuperscript{43}

3.1.13.1 WHO-ART

WHO Adverse Reaction Terminology is a highly refined terminology for coding clinical information in relation to drug therapy, used throughout the WHO Program by member countries and around the world by pharmaceutical companies and clinical research organizations.

WHO-ART has been developed over more than thirty years to serve as a basis for rational coding of adverse reaction terms. Because new drugs and new indications produce new adverse reaction terms, the structure of the terminology is flexible enough to allow new entries to be incorporated while maintaining its structure and without losing previous relationships.

WHO-ART covers most medical terms needed in adverse reaction reporting, but is still small enough to make it possible to print it out as a list which makes it easily usable for smaller companies and national centers\textsuperscript{43}.

Figure 3: WHO-ART Hierarchy
WHO-ART Hierarchy\textsuperscript{43}

**System Organ Class**

These are groups of adverse reaction Preferred terms pertaining to the same system-organ. A Preferred term can be allocated to a maximum of three different system-organ classes, e.g. respiratory depression is coded both under Respiratory disorders and Central nervous system disorders. The allocation of a Preferred term to system-organ classes is fixed and does not change with specific reports (Fig 3).

**High Level Term**

These are group terms of related or similar conditions, which are used for easy retrieval of information. E.g. thrombophlebitis leg and thrombophlebitis arm represent two different Preferred terms but are both grouped under thrombophlebitis as a high level term. All Preferred terms may not have been assigned a high level term (Fig 3).

**Preferred Term**

These are the principal terms used for describing drug adverse reactions (Fig 3).

**Included Term:**

These are terms closely related to Preferred terms. They are used to assist in finding the corresponding Preferred term for proper coding of the adverse reaction reported (Fig 3).
Figure 4: An example of WHO-ART Hierarchy

**WHO-ART Dictionary**

The WHO Drug Dictionary Enhanced is the world’s most comprehensive source of medicinal product information. It is used by:

- Pharmaceutical companies
- Clinical research organizations
- Drug regulatory authorities

They identify drug names, active ingredients and therapeutic use, in the course of their drug safety surveillance. WHO DD translates a drug name into useful information, which is used for coding and analysis of drug safety data – both pre- and post-marketing.

The majority of entries refer to prescription-only products, but some are over-the-counter (OTC) or pharmacist-dispensed preparations. Also entered in the dictionary are biotech and blood products, diagnostic substances and contrast media.

In order to increase coverage in more countries and gain faster access to information
about new releases, the UMC has entered a collaboration with IMS Health. The new WHO Drug Dictionary Enhanced is the result of this partnership. It contains data from the WHO Drug Dictionary as well as from the databases of IMS Health, and is produced using the same formats and principles as the previous WHO Drug Dictionary.

**The main benefits offered by the WHO Drug Dictionary Enhanced are:**

- Consistent, quality-assured, and up-to-date entry of information.
- A hierarchical structure allowing easy and flexible data-retrieval and analysis at different levels of precision (Fig 4)
- Chemical and therapeutic groupings - using the WHO drug record number system and ATC classifications.
- Available in software-independent electronic format for easy implementation in user systems.

Since the WHO Drug Dictionary Enhanced contains a higher-than-ever percentage of all product names that appear as co-medication, the need for manual investigations and fact-finding are reduced. Thus, it is more likely to find a direct match in the dictionary, which also reduces the need for making assumptions and guesses.

For hundreds of organizations around the world, the dictionary is a prime desk-reference for a wide range of tasks. New drugs are constantly introduced on the global market, and sometimes these products are modified. WHO-ART is made available in English, but has also been translated into German, French, Spanish, Portuguese and Italian. To help you keep track of these changes, the WHO Drug Dictionary Enhanced is updated four times per year. A paper print edition of WHO-ART is issued annually\(^\text{43}\).
3.1.13.2 MedDRA

MedDRA - the Medical Dictionary for Regulatory Activities - is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g., medical devices and vaccines). MedDRA is used to report adverse event data from clinical trials, as well as post-marketing and pharmacovigilance. Coding these data to a standard set of MedDRA terms allows health authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products.

MedDRA was developed by the International Conference on Harmonization (ICH) and is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as trustee for the ICH steering committee.

MedDRA is available in Czech, Dutch, English, French, German, Italian, Portuguese, Spanish, Japanese and Chinese. Updated MedDRA versions are released twice a year - in March and September. It is managed by MSSO (Maintenance and Support Services Organization WHO)

The MSSO - Maintenance and Support Services Organization - serves as the repository, maintainer, and distributor of MedDRA as well as the source for the most up-to-date information regarding MedDRA and its application within the biopharmaceutical industry and regulators. MedDRA subscribers submit proposed changes to the terminology. The MSSO includes a group of internationally based physicians who review all proposed subscriber changes and provide a timely response directly to the requesting subscriber.
Figure 5: MedDRA Hierarchy

- **SOC** - Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose
- **HLGT** – Subordinate to SOC, superordinate descriptor for one or more HLTs
- **HLT** – Subordinate to HLGT, superordinate descriptor for one or more PTs
- **PT** – Represents a single medical concept
- **LLT** – Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym (Note: All PTs have an identical LLT).

**WHO-ART to MedDRA bridging**

In 2008 UMC implemented MedDRA in the WHO database to make it as compatible with MedDRA as it has been with WHO-ART. All report data fields accepting WHO-ART have been made to allow either WHO-ART or MedDRA terms and all outputs will display both WHO-ART and MedDRA.
Vigibase now provides a global repository of MedDRA-coded safety data that can be used as a substantial tool for pharmacovigilance. The latest version is WHO-ART 09.1 to MedDRA 12.0. The mapping contains all WHO-ART preferred terms with a link to closest MedDRA terms which may be on either Low level or Preferred level, also giving codes for both WHO-ART and MedDRA terms. This mapping is 'one-sided' in that it links WHO-ART terms to MedDRA terms, but should not be used the other way around. The mapping is intended for WHO-ART users who may want to present or send data in MedDRA terminology to others and is provided as a txt-file free of charge to all WHO-ART and MedDRA customers.

3.1.13.3 ICD 10

ICD stands for International Classification of Diseases. ICD-10 was endorsed by the Forty-third World Health Assembly in May 1990 and came into use in WHO Member States as from 1994. The classification is the latest in a series which has its origins in the 1850s. The first edition, known as the International List of Causes of Death, was adopted by the International Statistical Institute in 1893. WHO took over the responsibility for the ICD at its creation in 1948 when the Sixth Revision, which included causes of morbidity for the first time, was published. The World Health Assembly adopted in 1967 the WHO Nomenclature Regulations that stipulate use of ICD in its most current revision for mortality and morbidity statistics by all Member States.

The ICD is the international standard diagnostic classification for all general epidemiological, many health management purposes and clinical use. These include the analysis of the general health situation of population groups and monitoring of the
incidence and prevalence of diseases and other health problems in relation to other variables such as the characteristics and circumstances of the individuals affected, reimbursement, resource allocation, quality and guidelines.

It is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. In addition to enabling the storage and retrieval of diagnostic information for clinical, epidemiological and quality purposes, these records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States.

It is available in the six official languages of WHO (Arabic, Chinese, English, French, Russian and Spanish) as well as in 36 other languages⁴⁵.

3.1.14 Uppsala Monitoring Centre⁴⁶

The World Health Organization set up its International Drug Monitoring Programme after the thalidomide disaster. Since 1978 the Programme has been carried out by The Uppsala Monitoring Centre in Sweden.

It is an independent foundation and a centre for international service and scientific research. Our priorities are the safety of patients and the safe and effective use of medicines in every part of the world. UMC meets these priorities by innovative research and development, and by providing data, reference, consultative and training resources to medicines regulatory agencies, health professionals, researchers and the pharmaceutical industry all over the world. With a track record of several decades, UMC is a reliable partner for the wide range of users of our high quality tools and services⁴⁶.
3.1.15 Overview of the Pharmacovigilance system for Adverse Drug Reaction Monitoring

Pharmacovigilance system deals with the collection of safety data of marketed drugs, its analysis for causality, seriousness, preventability, generation of signals, decisions regarding changes in policy and risk minimization or risk management plan. A well-organized drug safety management - pharmacovigilance service is a prerequisite for the early detection of the risks of drugs, prevention of adverse drug reactions (ADR) and aiding health professionals and patients to make the best benefit/risk assessment for safe and effective pharmacotherapy. The steps undertaken for adverse event reporting are:

a. Collection of the drug safety data:

Information about safety of drugs can be obtained through different methods of pharmacovigilance discussed above. The criteria for selecting the method depends on the local situation, experience, expertise, and resources available to achieve the objectives.

b. Review of literature:

Review of literature is performed for all suspected adverse events to get details whether the adverse drug reactions which are reported through the data collection process are listed in the literature.

c. Assessment of Adverse Drug Reactions (ADRs)

ADRs are assessed for
i. Causality as per the Naranjo scale or WHO criteria
ii. Seriousness as per the ICH criteria
iii. Severity as per Hartwig and Seigel scale
iv. Preventability as per Schumock and Thornton scale

d. Data entry into Vigibase

VigiBase is a unique collection of international drug safety data. The Vigibase data resource is the largest and most comprehensive in the world, and is developed and maintained by the Uppsala Monitoring Centre (UMC) on behalf of the World Health Organization. The data held is collected from countries participating in WHO Programme for International Drug Monitoring. A powerful search tool VigiSearch is to find individual case safety reports, ICSRs, in VigiBase. VigiMine is a statistical tool used within VigiSearch with vast statistical material calculated for all Drug-ADR pairs (combinations) available in VigiBase. The main features include the disproportionality measure (IC value) stratified in different ways. The output is generated in the form of tables which is easy to interpret.

e. Signal generation, signal strengthening, signal testing and evaluation

These are the three stages of signal detection. Signal generation consists of formation of hypotheses suggesting a possible association between exposure to drug and appearance of ADR. Thus signal generation is a method for highlighting potential adverse reactions and safety issues related the use of a particular drug that needs further investigation. This is achieved by calculating the IC value for different drug-ADR combinations. Signal generation and hypothesis formulation is followed by preliminary assessment of available data known as signal strengthening. Once the signal is generated and found to be of sufficient strength after preliminary data assessment it requires further testing and
evaluation to provide explanation in terms of strength of association and causal relationship called as the signal testing and evaluation stage.

f. Communication of information

Once a possible signal is generated the international monitoring centre publish in a drug reaction bulletin ‘Signals’ or medical journals to raise awareness of the reaction and also informs the national centers which communicate the information to the healthcare professionals, re assess the risk-benefit profile of a medicine, ask the pharma companies to make labeling changes (addition of contraindications, warnings, precautions and adverse reaction information to the product information and consumer medicine information), if required agencies request post marketing studies to be carried out by the Pharmaceutical company, further the national centers can recommend to amend the medicine’s product information, restrict the availability of the medicine or to remove the medicine from the market.

g. Develop risk minimization and risk management strategies for avoiding preventable ADRs

Risk minimization and risk management strategies are developed for avoiding preventable ADRs like reminder systems, performance linked assess system e.g. iPLEDGE program for isotretinoin48.
3.2: HAART Therapy

3.2.1 HIV Overview

HIV stands for human immunodeficiency virus. HIV attacks and destroys the infection-fighting CD4 cells of the immune system. Loss of CD4 cells makes it difficult for the immune system to fight infections. AIDS stands for acquired immunodeficiency syndrome. AIDS is the most advanced stage of HIV infection.

HIV is transmitted (spread) from one person to another through specific body fluids such as blood, semen, genital fluids, and breast milk. Having unprotected sex or sharing drug needles with a person infected by HIV are the most common ways HIV is transmitted.

Although it takes many years for symptoms of HIV to develop, a person infected with HIV can spread the disease at any stage of HIV infection. Detecting HIV during the earliest stages of infection and starting treatment well before symptoms of HIV develop can help people with HIV stay healthy. Treatment can also reduce the risk of HIV transmission.

3.2.2 Highly Active Antiretroviral therapy (HAART)

Highly Active Antiretroviral therapy (HAART) is the recommended treatment for HIV infection. HAART involves taking a combination (regimen) of three or more anti-HIV medications daily. HAART prevents HIV from multiplying and destroying infection-fighting CD4 cells. This helps the body fight off life-threatening infections and cancer. Although anti-HIV medications cannot cure HIV, people with HIV are enjoying healthy lives and are living longer.
Treatment with anti-HIV medications prevents HIV from multiplying and destroying the immune system. This helps the body to fight off life-threatening infections and cancers and prevents HIV from advancing to AIDS. Although it takes many years, without treatment HIV can advance to AIDS. To be diagnosed with AIDS, a person infected with HIV must either:

- **Have a CD4 count** less than 200 cells/mm\(^3\). (The CD4 count of a healthy person ranges from 500 to 1,200 cells/mm\(^3\). People infected with HIV with CD4 counts less than 500 cells/mm\(^3\) should begin ART.)

OR

- **Have an AIDS-defining condition.** (AIDS-defining conditions are serious and life-threatening illnesses. Having an AIDS-defining condition indicates that a person’s HIV infection has advanced to AIDS) \(^51\).

The recommend first-line regimen for adults and adolescents contain two NRTIs plus one NNRTI.

### 3.2.3 Choice of Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

**Lamivudine (3TC)** has been and remains pivotal to all first-line ARV regimens in resource-limited settings. It is a core component of the dual NRTI backbone in all ARV combinations. It has proved safe, has a favourable toxicity profile, is nonteratogenic, is effective against hepatitis B infection, is relatively cheap to produce and is widely available, including in fixed-dose combinations (FDCs) \(^51\).
Zidovudine (AZT) is included as a preferred first-line NRTI. It is generally well tolerated and widely available in some FDCs. Initial drug-related side-effects are headache and nausea, and it can also cause severe anaemia and neutropenia. Haemoglobin monitoring is recommended before and during treatment with AZT. This is particularly important in areas with a high prevalence of malaria, where anaemia is common. AZT is associated with metabolic complications, such as lactic acidosis and lipoatrophy, but to a lesser extent than d4T\(^5\).

Stavudine (d4T) is recognized as a life-saving drug that has played a crucial role in ART rollout, especially because of its availability in fixed-dose combinations (see Annex 10), the low cost of these FDCs and the clinical efficacy of the regimens recommended. d4T has also been preferred over AZT because of the requirement for limited or no laboratory monitoring. However, d4T has been consistently the NRTI most associated with lactic acidosis, lipoatrophy and peripheral neuropathy.\(^1\) The latter toxicities are cumulative and often irreversible, and have the potential to affect adherence in the long term. The stigmatization associated with lipoatrophy can result in withdrawal from or refusal to enrol in ART programmes. Programmes that are dependent on d4T-based regimens may need to follow through with their current strategies so that needed treatment for individuals is not delayed. Because of the current wide availability in FDCs and considerably lower prices, d4T-containing regimens may still remain the most accessible option for people in urgent need of treatment in resource-limited settings in the short to medium term. At the same time, WHO notes that it is important to begin planning to move away from d4T-containing regimens so as to avoid or minimize the predictable toxicities associated with this drug.
In the transition to safer first-line ARV choices, enhanced and closer monitoring for short-term and long-term d4T toxicities is recommended. This includes the training of health care workers and adequately informing patients of the signs and symptoms of lactic acidosis, lipoatrophy and peripheral neuropathy. Early recognition of d4T side-effects and switching to an alternative NRTI (such as AZT or TDF) may reduce the severity of these drug toxicities. d4T may be used as a substitute for AZT if intolerance occurs and TDF is unavailable\textsuperscript{51}.

### 3.2.4 Choice of Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

**Nevirapine (NVP)** is widely available (including in several FDCs) and is less costly than EFV. Moreover, significant experience has been gained with this drug at country level in resource-limited settings. However, a higher incidence of rash is associated with it than with EFV.\textsuperscript{18} NVP-related rash may be severe and life-threatening, and Stevens-Johnson syndrome may occur. NVP is also associated with a rare but potentially life-threatening risk of hepatotoxicity. This makes the drug less suitable for treating patients who use other hepatotoxic medications. The initiation of NVP at the same time as other new drugs that can also cause rash (e.g. co-trimoxazole) should be avoided where possible. In the case of severe hepatic or skin reactions, NVP should be permanently discontinued and not restarted (see Section 8). NVP is the preferred NNRTI for women if there is potential for pregnancy or during the first trimester of pregnancy, when EFV cannot be used because of its teratogenic effect. However, symptomatic NVP-associated hepatic toxicity or serious rash, while uncommon, is more frequent in women than in men, and more likely to be seen in antiretroviral-naive women with higher CD4 cell counts (above 250 cells/mm\textsuperscript{3}). Thus, NVP should be used with caution in women with CD4 counts between
250 and 350 cells/mm³. If it is used, careful monitoring is needed during the first 12 weeks of therapy provides more detailed information on dosing and preparations of the above-listed drugs. 

**Efavirenz (EFV)** can be used once daily and is generally well tolerated. However, it is relatively costly and currently less widely available than NVP. It is primarily associated with toxicities related to the central nervous system (CNS), teratogenicity and rash. Rash is generally mild, self resolving and usually does not require the discontinuation of therapy. The CNS symptoms typically abate after two to four weeks in the majority of patients. EFV should be avoided in patients with a history of severe psychiatric illness, when there is a potential for pregnancy (unless effective contraception can be assured) and during the first trimester of pregnancy. In these situations, NVP may be the better choice. EFV is the NNRTI of choice in individuals with TB/HIV coinfection who are receiving rifampicin-based TB therapy.

### 3.2.5 Early ARV toxicity

First-line drug toxicities fall into two categories: early, usually presenting in the first few weeks to months of therapy, and later. Common early and potentially severe toxicities are hypersensitivity to NNRTIs (EFV and NVP), normally occurring within the first few weeks of therapy, and AZT-related anaemia and neutropenia, typically presenting in the first few months of therapy. Many of the acute toxicities, if not identified early, can evolve into life-threatening and fatal events. Some of the higher mortality seen in the first six months of HAART undoubtedly relates to drug toxicity. Currently, limited
pharmacovigilance data are available for assessing the exact impact of HAART toxicity on early mortality\textsuperscript{51}.

### 3.2.6 Common ARV toxicities

Antiretroviral agents are responsible for a broad range of toxicities, ranging from low-grade intolerances that may be self-limiting to life-threatening side-effects. Differentiating between complications of HIV disease and ART toxicity (also known as adverse events) is sometimes difficult. Alternative explanations for a patient’s presenting symptoms should be considered before it is concluded that toxicity is ART-related. Considerations include intercurrent illness (e.g. hepatitis A virus infection in patients with symptoms of hepatitis, or malaria in patients with severe anaemia), or a reaction to medications other than ARVs, e.g. isoniazid-induced hepatitis or peripheral neuropathy, and rash induced by co-trimoxazole. Drug-related adverse events can occur early (the first few weeks or months of treatment) and late (after six months or more of treatment). Adverse events can vary in severity from mild to severe and life-threatening. ARV toxicity may be specific to the drug or to the class of drugs in use\textsuperscript{51}.

**Table 3: Common antiretroviral toxicities**

<table>
<thead>
<tr>
<th>Haematological toxicity</th>
<th>Drug-induced bone marrow suppression, most commonly seen with AZT (anaemia, neutropenia).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial dysfunction</td>
<td>Primarily seen with the NRTI drugs, including lactic acidosis, hepatic toxicity, pancreatitis, peripheral neuropathy, lipoatrophy, myopathy.</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>Nephrolithiasis, commonly seen with IDV. Renal tubular dysfunction is associated with TDF.</td>
</tr>
</tbody>
</table>
### Other metabolic abnormalities

More common with PIs. Include hyperlipidaemia, fat accumulation, insulin resistance, diabetes and osteopenia.

### Allergic reactions

Skin rashes and hypersensitivity reactions, more common with the NNRTI drugs but also seen with certain NRTI drugs.

### 3.2.7 HIV/TB Co-Infection

Worldwide, tuberculosis is the most common opportunistic infection among people with HIV infection. In addition to its frequency, tuberculosis is also associated with substantial morbidity and mortality. Despite the complexities of treating two infections requiring multidrug therapy at the same time, antiretroviral therapy can be life-saving among patients with tuberculosis and advanced HIV disease. HIV infected persons with TB often require ART, and WHO recommends that ART be given to all patients with extrapulmonary TB (stage 4) and all those with pulmonary TB (stage 3) unless the CD4 count is above 350 cells/mm³. ART reduces both case-fatality rates and the incidence of TB and recurrent TB. Antiretroviral therapy in individuals undergoing treatment for TB merits special consideration because co-management of HIV and TB is complicated by: drug interactions between rifampicin and both the NNRTI and PI classes; the immune reconstitution inflammatory syndrome (IRIS); pill burden; overlapping toxicities; and adherence issues. Active TB can be present when ART needs to be initiated or can present in patients receiving first-line or second-line therapy. The treatment of active TB remains a priority for patient care. Collaboration between TB and HIV programmes is essential for the delivery of an integrated package of HIV and TB services.
The recommended standard first-line ART regimen comprises two NRTIs plus one NNRTI. There are few drug interactions with TB drugs and the NRTI backbone and no specific changes are recommended. The situation is more complex with the NNRTI class because NNRTI levels are reduced in the presence of rifampicin. However, accumulating data support the use of first-line NNRTI-containing antiretroviral regimens in patients receiving rifampicin-containing treatment for TB. Here EFV is the preferred option, because the interactions with rifampicin are easier to manage; but the use of EFV may be limited by its restrictions in pregnant women or women of childbearing potential. NVP is an alternative agent, but carries the risk of hepatotoxicity, particularly in persons with higher CD4 counts or for whom no CD4 count is available. The use of a triple NRTI regimen is emerging as an additional option for first-line ART in TB patients with HIV-2 infection. An initial PI-based regimen can also be considered in HIV-2 infection, with the caveat that it will compromise second-line treatment options. Two NRTIs + efavirenz.

3.2.8 Concomitant use of treatment for tuberculosis and antiretroviral therapy
Concomitant use of treatment for tuberculosis and antiretroviral therapy is complicated by the adherence challenge of polypharmacy, overlapping side effect profiles of antituberculosis drugs and antiretroviral drugs, immune reconstitution inflammatory syndrome, and drug-drug interactions. The key interactions, and the focus of this document, are those between the rifamycin antibiotics and four classes of antiretroviral drugs: protease inhibitors, non-nucleoside reverse-transcriptase inhibitors [NNRTI], CCR5-receptor antagonists, and integrase inhibitors. Only two of the currently available antiretroviral drug classes, the nucleoside analogues (other than zidovudine) and
enfuvirtide (a parenteral entry inhibitor) do not have significant interactions with the rifamycins.

Despite the complexity of these drug interactions, the key role of the rifamycins in the success of tuberculosis treatment mandates that the drug-drug interactions between the rifamycins and antiretroviral drugs be managed, not avoided by using tuberculosis treatment regimens that do not include a rifamycin or by withholding antiretroviral therapy until completion of anti-tuberculosis therapy among patients with advanced immunodeficiency. In randomized trials, regimens without rifampin or in which rifampin was only used for the first two months of therapy resulted in higher rates of tuberculosis treatment failure and relapse. The sub-optimal performance of the regimen of two months of rifampin (with isoniazid, pyrazinamide, and ethambutol) followed by 6 months of isoniazid + ethambutol was particularly notable among participants with HIV co-infection 5. Therefore, patients with HIV-related tuberculosis should be treated with a regimen including a rifamycin for the full course of tuberculosis treatment, unless the isolate is resistant to the rifamycins or the patient has a severe side effect that is clearly due to the rifamycins. Furthermore, patients with advanced HIV disease (CD4 cell count < 100 cells/mm3) have an increased risk of acquired rifamycin resistance if treated with a rifamycin-containing regimen administered once or twice weekly. The rifamycin-based regimen should be administered daily (5-7 days per week) for at least the first 2 months of treatment among patients with advanced HIV disease53.
3.2.9 Rifampin and Antiretroviral Therapy

The most important drug-drug interactions in the treatment of HIV-related tuberculosis are those between rifampin and the NNRTIs, efavirenz and nevirapine. Rifampin is the only rifamycin available in most of the world, and initial antiretroviral regimens in areas with high rates of tuberculosis consist of efavirenz or nevirapine (in combination with nucleoside analogues). Furthermore, because of its potency and durability in randomized clinical trials, efavirenz-based therapy is a preferred option for initial antiretroviral therapy in developed countries\textsuperscript{53}.

**Two NRTIs + efavirenz**

EFV blood levels are decreased in the presence of rifampicin. This can be overcome by a dose increase of 600 mg to 800 mg daily. Emerging evidence does not show any benefit in increasing the EFV dose to 800 mg/daily in patients weighing under 60 kg and receiving both EFV and rifampicin. While awaiting more data on EFV dosing for persons weighing 60 kg and above, WHO recommends the standard 600-mg dose of EFV. Because of concerns related to teratogenicity, EFV should not be used in women of childbearing potential without adequate contraception or in women who are in the first trimester of pregnancy\textsuperscript{54}.

**Two NRTIs + nevirapine**

NVP levels are also decreased in the presence of rifampicin. However, given the high therapeutic index of NVP and the recent studies in South Africa and Thailand showing good short-term outcomes in antiviral activity and few adverse events in patients receiving both drugs, standard NVP dosing is recommended. This area requires further
investigation as there is large interpatient variability in NVP levels among HIV-infected persons, independently of any rifampicin interaction. Because of concerns about safety, close clinical and laboratory monitoring of liver enzymes at weeks 4, 8 and 12 is advised for all patients receiving NVP plus rifampicin. There are concerns about the risk of symptomatic or fatal hepatitis in women with CD4 counts between 250 and 350 cells/mm³. The additional influence on the liver toxicity of rifampicin containing regimens in this population is not known. Until further data are available, nevirapine containing regimens should only be considered in life-threatening situations and when no alternative is available for women on rifampicin-containing regimens who have CD4 cell counts in the range 250 to 350 cells/mm³ and need to start ART.

However in the ART centers in India Nevirapine is not prescribed to HIV patients with TB co infection⁵⁴.

**Table 4: Regimens for the concomitant treatment of TB and HIV infection**

<table>
<thead>
<tr>
<th>Combined regimen for treatment of HIV and TB</th>
<th>PK effect of the Rifamycin</th>
<th>Tolerability / Toxicity</th>
<th>Antiviral activity when used with Rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz-based ART with rifampin-based TB treatment</td>
<td>Well characterized, modest effect</td>
<td>Low rates of discontinuation</td>
<td>Excellent</td>
</tr>
<tr>
<td>Nevirapine-based ART with Rifampin-based TB treatment</td>
<td>Moderate effect</td>
<td>Concern about hepatotoxicity when used with isoniazid, rifampin and pyrazinamide</td>
<td>Favorable</td>
</tr>
</tbody>
</table>
3.3: ADRs reported to psychotropic drugs

3.3.1 Definition of Psychiatric disorder
Way to define a psychiatric disorder or mental disorder is as a clinically significant psychological or behavioral syndrome that causes significant (subjective) distress, (objective) disability, or loss of freedom: an is not merely a socially deviant behavior or an expected response to a stressful life event (e.g. loss of a loved one). Conflicts between the society and individual are not considered psychiatric disorder. A psychiatric disorder should be a manifestation of behavioral, psychological and/or biological dysfunctions in that patient.\(^5\)

3.3.2 Classification of Psychiatric disorders (ICD-10)\(^5\)

- **F00-F09**: Organic including symptomatic, mental disorders, such as delirium, dementia, organic domestic syndrome, and other mental disorders.
- **F10-F19**: Mental and Behavioral disorders due to psychoactive substances use, dependence syndrome, withdrawal state, amnestic syndrome and psychotic disorders due to psychoactive substance use
- **F20-F29**: Schizophrenia, Schizotypal and Delusional Disorders, such as schizophrenia, schizotypal disorder, persitant delusional disorder, acute and transient psychotic, induced delusional disorder, and schizo-affective disorders
- **F31-F39**: Mood (Affective) Disorders, such as manic episode, depressive episode, bipolar affective disorder, recurrent depressive disorder, and persitant mood disorder
- **F40-F48**: Neurotic, Stress-related and Somatoform Disorders, such as anxiety disorder, phobic anxiety disorder, obsessive-compulsive disorder. Dissociative
conversion) disorder, somatoform disorders, reaction to stress and adjustment disorders, and other neurotic disorders

- **F50-F59**: Behavioral Syndromes Associated with Physiological Disturbances and Physical Factors, such as eating disorder, non-organic sleep disorders, sexual dysfunction (not caused by organic disorder or disease), mental and behavioral disorders with puerperium and abuse of non-dependance producing substances.

- **F60-F69**: Disorders of adult personality and Behavior, such as specific personality disorder, enduring personality changes, habit and impulse disorders, gender-identity disorder, disorders of sexual preference, and behavioral disorders associated with sexual development and orientation

- **F70-F79**: Mental Retardation, including mild, moderate, severe and profound mental retardation.

- **F80-F89**: Disorders of Psychological Development, such as specific developmental disorders of speech and language, specific developmental disorders of scholastic skills, specific developmental disorders of motor function, mixed specific developmental disorders, and persuasive developmental disorders

- **F90-F98**: Behavioral and Emotional Disorders with onset Usually Occurring in Childhood and Adolescence, such as hyperkinetic disorders, conduct disorders, mixed disorders of conduct and emotions and other disorders

- **F99**: Unspecific Mental Disorders
3.3.3 **Psychotropic Drugs:** reduce many symptoms of mental dysfunction. Results are seen in changes of emotions and thought process and behaviors\(^\text{57}\).

3.3.4 **Classification of psychotropic drugs\(^\text{58}\)**

Depending on the primary use the psychotropic drugs may be majorly grouped into

1. Antipsychotics

2. Antidepressants

3. Antianxiety

3.3.4.1 **Antipsychotics**

1. Phenothiazines
   - *Aliphatic side chain:* Chlorpromazine, Triflupromazine
   - *Piperidine side chain:* thioridazine
   - *Piperazine side chain:* Trifuperazine, Fluphenazine

2. Butyrophenones:
   - Haloperidol, Trifluperidol, Penfluperidol

3. Thioxanthenes:
   - Flupenthixol

4. Other heterocyclics:
   - Pimodine, Loxapine

5. Atypical neuroleptics
   - Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole, Ziprasidone
First Generation Antipsychotics: Discovered in the 1950’s while researching for antihistamines to treat allergies. Reduced psychotic symptoms, especially in schizophrenic patients by reducing dopamine. For example they helped correct confusion, hallucinations, and delusions: positive Symptoms. Example: phenothiazines, thioxanthenes.

Atypical Antipsychotics: 1990’s brought newer drugs: target dopamine receptors in the limbic system. Results in therapeutic effect with less or no motor side effects. Additionally works on 5-HT 2 receptors for Serotonin. Help both positive and negative symptoms of schizophrenia.

Mechanism of Action

- Antipsychotic drugs are effective in treating psychosis due to their action on the D2-receptors (block)
- Atypical antipsychotics have a weak D2 blocking but potent 5-HT2 antagonistic activity

Figure 6: Decision tree for evaluating psychosis\textsuperscript{51}
Uses:
• Used to treat schizophrenia and psychotic symptoms of other disorders
• Schizophrenia is a severe chronic disorder
• Positive symptoms: hallucinations, and delusions
• Negative symptoms: amotivation, poverty of speech, flat affect
• Disorganized symptoms: speech, thought, and behavior
• Mania

Table 5: Daily dose of antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Daily Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Phenothiazines</td>
<td>100-800</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Phenothiazines</td>
<td>100-400</td>
</tr>
<tr>
<td>Trifuperazine</td>
<td>Phenothiazines</td>
<td>2-20</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Butyrophonones</td>
<td>2-20</td>
</tr>
<tr>
<td>Trifluperidol</td>
<td>Butyrophonones</td>
<td>1-8</td>
</tr>
<tr>
<td>Flupenthixol</td>
<td>Thioxanthenes</td>
<td>1-10</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Other heterocyclics</td>
<td>2-100</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Atypical neuroleptics</td>
<td>2-12</td>
</tr>
<tr>
<td>Olanzepine</td>
<td>Atypical neuroleptics</td>
<td>2.5-10</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Atypical neuroleptics</td>
<td>50-400</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Atypical neuroleptics</td>
<td>50-400</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Atypical neuroleptics</td>
<td>5-30</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Atypical neuroleptics</td>
<td>40-160</td>
</tr>
</tbody>
</table>
Adverse drug reactions of antipsychotics:

1. CNS
   - Drowsiness
   - Lethargy
   - Mental confusion
   - Increased appetite and weight gain

2. CVS
   - Postural hypotension
   - Palpitation
   - Inhibition of ejaculation
   - QT prolongation
   - Cardiac arrhythmias

3. Anticholinergic
   - Dry mouth
   - Blurring of vision
   - Constipation
   - Urinary hesitancy in elderly males
   - Clozapine induced hyper salivation

4. Endocrine
   - Hyperprolactinemia (due to D2 blockade)
   - Amenorrhoea
   - Infertility
   - Galactorrhoea
• Gynacomastia

5. Extrapyrimidal

• Parkinsonism
• Acute muscular dystonias
• Akathisia
• Malignant neuroleptic syndrome
• Tardive dyskinesia

6. Miscellaneous

• Weight gain
• Blood sugar and lipids tend to rise

3.3.4.2 Antidepressants

Classification of Antidepressants\textsuperscript{58}

a. Reversible inhibitors of MAO-A (RIMAs)
   - Moclobemide, Clorgyline

b. Tricyclic antidepressants (TCAs)

• NA+5-HT reuptake inhibitors
  - Imipramine, Amitriptiline, Trimipramine, Doxepine, Dothiepin, Clomipramine
• Predominantly NA uptake inhibitors
  - Desipramine, Nortriptyline, Amoxapine, Reboxetine
c. Selective serotonin reuptake inhibitors (SSRIs)
   - Fluoxetine, Fluvoxamine, Paroxetine, Sertaline, Citalopram, Escitalopram

d. Atypical antidepressants
   - Trazodone, Miniaserin, Mirtazepam, Venlafexine, Duloxetine

Mechanism of action:
Predominant action of antidepressants is to increase the catecholamine levels in the brain.
MAO is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines.
MAO-A preferably deaminates 5-HT and is inhibited by moclobemide and clorgyline.
TCAs and related drugs inhibit active reuptake of biogenic amines NA and 5HT into their neurons and thus potentiate them.
SSRIs were introduced to overcome the major limitations of conventional TCAs which were:

- Frequent anticholinergic, cardiovascular and neurological side effects
- Relatively low safety margin, hazardous in overdose, fatalities common
- Lag time of 2-4 weeks before antidepressant action manifests
- Significant number of patients respond incompletely and some do not respond
- To overcome this SSRIs were introduced in the 1980s which selectively inhibit membrane associated SERT (serotonin transporter)

Atypical antidepressants
- Mianserin: blocks presynaptic alpha 2 receptors- increase release and turnover of NA in the brain which may be responsible for antidepressant effect
• Venlafaxine: A novel antidepressant is a serotonin and noradrenaline reuptake inhibitor

Uses:
• Endogeneous (major) depression
• Obsessive compulsive and phobic states
• Anxiety disorders
• Neuropathic pain
• Attention deficit-hyperactivity disorder
• Enuresis
• Migrane

Table 6: Daily dose of antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Daily Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moclobemide,</td>
<td>Reversible inhibitors of MAO-A</td>
<td>150 mg BDS TDS (max 600mg / day)</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tricyclic antidepressants</td>
<td>50-200</td>
</tr>
<tr>
<td>Amitriptiline,</td>
<td>Tricyclic antidepressants</td>
<td>50-200</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Tricyclic antidepressants</td>
<td>50-150</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>20-50</td>
</tr>
<tr>
<td>Sertaline</td>
<td>SSRI</td>
<td>50-200</td>
</tr>
<tr>
<td>Citalopram</td>
<td>SSRI</td>
<td>20-40</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>SSRI</td>
<td>10-20</td>
</tr>
<tr>
<td>Miniaserin</td>
<td>Atypical antidepressants</td>
<td>30-100</td>
</tr>
<tr>
<td>Mirtazepam</td>
<td>Atypical antidepressants</td>
<td>15-45</td>
</tr>
<tr>
<td>Venlafexine</td>
<td>Atypical antidepressants</td>
<td>75-150</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Atypical antidepressants</td>
<td>30-80</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Atypical antidepressants</td>
<td>50-200</td>
</tr>
</tbody>
</table>
Adverse drug reactions common with TCAs\textsuperscript{58}

1. **Anticholinergic**
   - Dry mouth
   - Bad taste
   - Constipation
   - Epigastric distress
   - Urinary retention
   - Blurred vision

2. **Others**
   - Palpitation
   - Sedation
   - Mental confusion
   - Weakness
   - Increased appetite
   - Weight gain
   - Sweating
   - Fine tremors
   - Postural hypotension
   - Cardia arrhythmias especially in patients with ischaemic heart disease

**Adverse drug reactions common with SSRIs**

Serotonin syndrome precipitating as agitation, restlessness, sweating, twitching followed by convulsions can be precipitated when any serotonergic drug is taken by patient
receiving SSRIs. Some degree of tolerance has been noted with SSRIs by some patients after months of use\textsuperscript{58}.

\textbf{Adverse drug reactions common with atypical antidepressants}

1. Mianserin: Blood dyscrasias and liver dysfunction
2. Venlafaxine: nausea, sweating, dizziness, and impotence

\textbf{3.3.4.3 Antianxiety Drugs}

\textbf{Classification of Antianxiety}\textsuperscript{58}

1. Benzodiazepines:
   - Diazepam, Chlordiazepoxide, Oxazepam, Lorazepam, Alprazolam

2. Azaspirones:
   - Buspirone, Ispapirone, Gepirone

3. Sedative anti histaminics:
   - Hydroxyzine

4. Beta blocker:
   - Propranolol

\textbf{Mechanism of action}

GABA exerts an inhibitory effect on neurons. These drugs enhance this effect and produce a sedative effect. Therefore reduce anxiety. The most common used drugs here are the \textbf{Benzodiazepines}

\textbf{Benzodiazepine}

- Used for anxiety, panic disorders, alcohol withdrawal, muscle spasm, sedation, insomnia, and epileptics/seizures
• Use only short term because of dependency issues

**Side Effects:**
- Drowsiness, confusion, sedation, and lethargy, light headedness, vertigo

**Toxic Effects:**
- Respiratory depression esp. with alcohol use

**Contraindications:**
- Combination with other CNS depressants
- Renal or hepatic dysfunction
- History of drug abuse or addiction
- Depression and suicidal tendencies

**Dose:**
- Chlordiazepoxide: 80-200 mg/day
- Diazepam: 40-80mg/day
3.4: Kala-Azar and Pharmacovigilance of Miltefosine

3.4.1 Kala-Azar Overview

Kala-Azar (Visceral Leishmaniasis) is a deadly disease caused by the parasitic protozoa *Leishmania donovani* and transmitted to humans by the bite of infected female sand fly, *Phlebotomus argentipes*. The amastigote form of the parasite invades the Reticulo endothelial system of humans. It lowers immunity, causes persistent fever, anemia, liver and spleen enlargement, progressive weight loss and if left untreated, it leads to death. The vector thrives in cracks and crevices of mud plastered houses, poor housing conditions, heaps of cow dung, in rat burrows, in bushes and vegetations around the houses\(^59\).

There are four main types of the disease:

- In cutaneous forms, skin ulcers usually form on exposed areas, such as the face, arms and legs. These usually heal within a few months, leaving scars.

- Diffuse cutaneous leishmaniasis produces disseminated and chronic skin lesions resembling those of lepromatous leprosy. It is difficult to treat.

- In mucocutaneous forms, the lesions can partially or totally destroy the mucous membranes of the nose, mouth and throat cavities and surrounding tissues.

- Visceral leishmaniasis, also known as Kala-Azar, is characterized by high fever, substantial weight loss, swelling of the spleen and liver, and anaemia. If left untreated, the disease can have a fatality rate as high as 100% within two years\(^60\).
3.4.2 Diagnosis and treatment of Kala-Azar

Diagnosis and treatment of Kala-Azar has been difficult. It is done by clinical features of the disease in an endemic area confirmed by either demonstration of the parasite in the splenic aspirate or indirect tests which is an invasive and risky procedure\textsuperscript{52}. Presently the rk 39 test kit is widely used which is performed on peripheral blood and used in the community\textsuperscript{61}.

The standard drug for the treatment of VL is a pentavalent antimonial, sodium antimony gluconate (SAG) administered parenterally. The second-line drug, amphotericin B desoxycholate, is also parenteral and is more toxic as compared to SAG. Liposomal amphotericin B is effective and safe, but it is very expensive even for developed countries and prohibitively so for regions of endemicity. Miltefosine (hexadecylphosphocholine) is an oral drug that was originally studied as an antitumor agent. Subsequent to the serendipitous laboratory finding that miltefosine was active against \textit{Leishmania in vitro} and, after oral administration in laboratory animals, the drug was developed in a public-private partnership for the treatment of visceral leishmaniasis or Kala-Azar. In a phase three trial involving Indian adults, miltefosine given at a dosage of 2.5 mg/kg per day for 28 days cured 282 (97\%) of 291 evaluable patients who remained parasitologically and clinically free even after 6 months of follow-up.

The phase-IV trial of miltefosine was undertaken by ICMR for testing the applicability of the drug under routine clinical conditions. The cure rates during this operational trial were found to be high. The drug is registered with the Drug Controller General of India. The toxicity associated with the drug is minor.
Considering the experience gained in the use of oral drug miltefosine, the Expert Committee, under the Chairmanship of Director General Health Services, GOI recommended that the drug can be used for Kala-Azar treatment under the Kala-Azar elimination programme\textsuperscript{62}. Miltefosine can be given on an outpatient basis and has been found to be effective in more than 90% of VL cases.

3.4.3 Problem Statement Global:

It is estimated that 350 million people in 88 countries are at the risk of developing the disease. About 500,000 people suffer from it. (Fig. 7)

South East Asia Region

About 200 million people are estimated to be at risk from this disease. The estimated number of cases is about 100,000 distributed in India, Bangladesh and Nepal. However, it is felt by many authorities that the number of sufferers may be a few times that number\textsuperscript{59}.

India

165 million people are estimated to be at risk. The reported number of cases is around 20,000 and number of deaths about 200 per year. Estimated number of cases is much higher. Bihar state is the worst affected with 33 districts endemic. It is also found in the neighboring states of West Bengal with ten districts affected, Jharkhand with five districts endemic and Uttar Pradesh with four\textsuperscript{59}. 
3.4.4 Memorandum of article signed for Kala-Azar

The Health Ministers of three Member States of WHO’s South-East Asia Region, India, Nepal and Bangladesh signed a Memorandum of Understanding pledging to collaborate to eliminate Visceral Leishmaniasis (Kala-Azar) from their countries on 18 May 2005. In terms of the program it would mean reaching a prevalence of less than one case per ten thousand populations at the sub district level in India, Upazila in Bangladesh and district level in Nepal by the year 2015$^{59}$.

This is to be achieved by using the new diagnostic tool, rk 39 and the new oral drug, Miltefosine along with Amphotericin, Paromomycin and their combinations.