COMPARATIVE STUDY OF ANTI-TUBERCULAR DRUGS: A COMPREHENSIVE REVIEW

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Abstract :-

Drug resistance, co-infections, and social determinants of health are some of the elements that make tuberculosis (TB) a persistent danger to world health. Mycobacterium tuberculosis is the causative agent of tuberculosis (TB), which mainly affects the lungs but can potentially affect other organs. Poverty, malnourishment, crowded living situations, and immunocompromised conditions like HIV/AIDS are risk factors for tuberculosis. Cough, fever, weight loss, and night sweats are some of the symptoms of tuberculosis (TB), though these might change based on the infection site. Rapid molecular assays, imaging studies, microbiological testing, and clinical evaluation are usually used in the diagnosis process. Multidrug therapy is used for six to nine months of treatment; lengthier and more complicated regimens are needed for drug-resistant TB. The etiology, symptoms, diagnosis, pathophysiology, epidemiology, and therapy of both pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) have all been covered in this review article. The first-line medications are isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. Our goal was to assess the factors that influence pharmacokinetic variance and to characterize the pharmacokinetics of rifampin, isoniazid, pyrazinamide, and ethambutol in TB patients who were started on first-line therapy regimens. Each drug's 2-hour level, plasma concentration-time, and area under the curve for 0–8-hour profiles were determined.

Key words :- Tuberculosis, Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, Streptomycin.

Introduction

Robert Koch discovered the tubercle bacillus, also called Mycobacterium Tuberculosis, to be the causative agent of tuberculosis in 1882. The TB epidemic has seemingly continued to grow over the world since his discovery. One of the leading causes of death globally, tuberculosis is a highly contagious airborne disease. Due to its diverse presentation, tuberculosis is classified as either extra-pulmonary TB (EPTB) or pulmonary TB (PTB) depending on its clinical manifestation. When TB affects organs other than the lungs, such as the pleura, lymph nodes, abdomen, genitourinary system, skin, joints, bones, or meninges, it is referred to as EPTB. A patient is diagnosed with pulmonary TB (e.g. military TB) if they additionally have tubercular lesions in the lung parenchyma in addition to EPTB. TB pleural effusion without radiographic abnormalities in the lung is known as EPTB if the patient has intra-thoracic mediastinal and/or hilar lymph node TB. With only slight adjustments to the reagents and interpretative standards, the diagnostic Mantoux

skin test, which was created in 1909, is still used today. Another method for diagnosing tuberculosis is the Interferon-gamma release assay (IGRA), which was created in 2014. Both tests have predictive and diagnostic limitations that necessitate a deep comprehension of interpretation standards. Sputum smear microscopy, which uses Ziehl-Neelsen Stain to stain the TB bacteria, is a very effective and popular approach for diagnosing tuberculosis. However, the main drawbacks of this technique are its limited sensitivity and inability to distinguish Mtb from other acid-fast bacilli. Sputum culture, which uses Lowenstein-Jensen medium to cultivate the TB germs, is a highly sensitive and specific diagnostic technique for tuberculosis under smear spectroscopy. Yet because Mtb is a slow-growing organism, it takes at least two weeks—and occasionally six or eight weeks—for the colonies to form, which causes additional delays in diagnosis and treatment. Lastly, a number of symptoms that enable clinical diagnosis appear in 5–10% of TB-infected people. Pleuritic cheat pain, low grade fever, persistent productive cough, haemoptysis, drowsiness, appetite loss, night sweats, and weight loss are some of the clinical signs of active pulmonary tuberculosis.

Etiology :-

Closely related species that can infect humans and animals are members of the Mtb family, sometimes referred to as the tuberculosis complex. Actually, the term "tuberculosis" solely refers to the illness brought on by Mycobacterium tuberculosis. The closely related mycobacteria M. bovis, M. africanum, and M. microti can infrequently cause similar illness. The term "Mycobacterium tuberculosis complex" refers to these three microorganisms as well as M. tuberculosis and other uncommon mycobacteria. Mtb are bacilli that are aerobic, non-motile, and do not generate spores. Their acid-fast staining ability is attributed to the lipids' very high concentration in the cell wall, which also probably plays a role in immunomodulation and virulence. Inhaling airborne particles harboring M. tuberculosis is the primary cause of tuberculosis. Coughing, sneezing, and other forced respiratory movements by individuals with active pulmonary or laryngeal TB whose sputum contains a high number of organisms are the main ways they spread. Because cavitary lesions contain a lot of bacteria, people with them are particularly contagious. The likelihood of transmission is increased by the possibility that droplet nuclei containing tubercle bacilli may linger in room air currents for several hours. With a generation time of roughly 20 hours, tuberculosis is a slow-growing bacterium. On solid media, visible development typically takes three to eight weeks.

Worldwide, isolates exhibit genetic heterogeneity, which could contribute to variations in virulence. Environmental aspects are also significant. Frequent or extended exposure to untreated individuals who are producing a high number of tubercle bacilli in crowded, poorly ventilated, enclosed spaces increases the risk of transmission; as a result, those living in poverty or in institutions are more vulnerable. Healthcare professionals that work closely with ongoing cases are at higher risk. Although more accurate human-to-animal experiments indicate that transmission stops a few days after beginning therapy, epidemiologic studies of household contacts indicate that transmission stops two weeks after patients begin receiving effective treatment. In the past, consumption of milk or milk products tainted with M. bovis was a prevalent cause of tuberculosis (TB) of the tonsils, lymph nodes, abdominal organs, bones, and joints. They can cause progressive and subacute disease since they are intracellular infections. Infected cells can potentially harbor dormant bacteria that may or may not produce illness. Research on the molecular and immunologic processes underlying dormancy and reactivation is crucial, yet it is still unclear.

Epidemiology:-

TB is still a major global health issue that affects public health and healthcare systems all over the world. The World Health Organization (WHO) estimates that 10 million people contracted tuberculosis (TB) in 2019, and the disease was responsible for about 1.4 million fatalities.

Every year, the WHO releases a report detailing the state of the epidemic and the advancements made toward the objectives of the WHO End TB Strategy. Globally, TB was expected to have killed 1.3 million people in 2022, down from 1.4 million in 2020 and 2021. In 2022, almost 7.5 million people received a TB diagnosis; 46% of these individuals reside in Southeast Asia, 23% in Africa, and 18% in the Western Pacific. Not all communities are equally affected by tuberculosis (TB), with some areas experiencing a disproportionate amount of the disease's burden. According to the WHO, the biggest number of TB cases worldwide occur in South-East Asia and Africa, with China and India alone responsible for almost 40% of the global TB burden.

Currently, 10.6 million individuals worldwide—5.8 million men, 3.5 million women, and 1.3 million children—are living with active tuberculosis. Approximately 25% of people worldwide are infected, and 5–10% of them go on to acquire active TB. After 27 years of declining numbers, this 16% gain comes on top of annual increases since 2020. A major public health concern is drug-resistant tuberculosis. Approximately 17% of TB cases who have already received treatment and 13% of new infections worldwide are sensitive to rifampin (RIF) and isoniazid (INH). 10.8 million cases of tuberculosis were reported worldwide in 2023, up from 10.7 million in 2022, 10.4 million in 2021, and 10.1 million in 2020.

In 2023, the WHO areas of South-East Asia (45%), Africa (24%), and the Western Pacific (17%) had the highest rates of tuberculosis cases, while the Eastern Mediterranean (86%), the Americas (3.2%), and Europe (2.1%) had relatively lower rates. Eight of the 30 countries with the highest estimated TB burdens accounted for more than two-thirds of the global total, with India accounting for 26%, Indonesia for 10%, China for 6.8%, the Philippines for 6.8%, Pakistan for 6.3%, Nigeria for 4.6%, Bangladesh for 3.5%, and the Democratic Republic of the Congo for 3.1%. 56% of the global total came from the top five nations.

Taxonomy and Description of the genus :-

Mycobacterium Tuberculosis is

Family - Mycobacteriaceae

Order - Actinomycetales

Class – Actinomycetes

Genus - Mycobacterium

Gordomia, Tsukamurella, Nocardia, and Rhodococcus are genera that are closely related to Mycobacterium.

Pathophysiology:-

Mycobacterium tuberculosis infection is the cause of tuberculosis. Although it mostly affects the lungs, this slow-growing, acid-fast bacillus can also damage other body organs. M. tuberculosis virulence factors and the host immune response interact intimately in the pathophysiology of tuberculosis (TB), resulting in the disease's distinctive clinical appearance. When active TB patients cough, sneeze, or speak, they release aerosol droplets that contain M. tuberculosis, which is how TB is spread. Droplet nuclei may settle on the mucosa of the upper airways, where the infection is unlikely to establish itself, or they may enter the alveoli, where pathological processes may start. In the presence of host immunomodulatory systems, the bacillus may be eliminated, remain dormant, or develop into active tuberculosis disease, depending on intricate and poorly understood pathogen virulence factors.

There are three stages of tuberculosis:

- primary infection
- latent infection
- active infection.

The TB germs enter the host's lungs through the respiratory system after being inhaled. The tubercle bacilli are then absorbed by alveolar macrophages as the host's innate immune system steps in to stop the infection.
Alveolar macrophages play a key role in immunomodulation. The macrophages absorb the bacilli and either eliminate them or create the primary infection.
Following the recruitment of lymphocytes to the infection site, a formation of immune cells comes in an effort to contain the bacteria and prevent its further growth, starting a cell-mediated immune response. At this stage, the host is still asymptomatic, and the TB bacteria may either completely disappear or enter a state of latency within the granuloma. However, the illness quickly develops into active TB with clinical symptoms when immunity is compromised.
The bacilli are found in the granuloma of the majority of immunocompetent adults, resulting in a latent infection. The bacilli can spread lymphohematogenously across the lung and to almost any other organ, evading immunologic restrictions. Dormancy in M. tuberculosis is not always the same as latent TB. Individuals with latent TB may alternate between subclinical TB illness and periods of dormancy.
By upsetting the equilibrium between the influx and outflow of lipid particles from the serum and their sequestration, M. tuberculosis-induced deregulation of host lipid metabolism was discovered to be a key factor in the development of the disease.
The development of foam cells, which enable bacterial persistence and ultimately lead to the deposition of caseum in the granuloma, is encouraged by this disruption in lipid metabolism. Furthermore, it has been shown that mycolic acids (Mas), the main lipid components of the strong cell wall of Mycobacterium tuberculosis (M. tuberculosis) and crucial for the growth and survival of the mycobacterium, aid in the differentiation of macrophages into foam cells. The tubercle bacilli are encased and protected by the ensuing caseous lesions, which act as reservoirs and keep the germs dormant.
Reactivation of a latent focus of infection is the most frequent process resulting in active illness. Although previously infected individuals are usually immune to exogenous reinfection, reinfection can occur if a person has a damaged immune system or is exposed to a high inoculum. With significant therapeutic and epidemiologic consequences, it might be difficult to determine whether a person with a history of TB has relapsed as a result of endogenous reinfection or a recently acquired exogenous reinfection.

Signs and Symptoms :-

The host's immune system, the location and severity of the infection, and the existence of underlying health conditions are only a few of the variables that might affect the symptoms of tuberculosis. A chronic cough that lasts longer than two weeks and may produce sputum that is frequently purulent or bloody is one of the typical signs of pulmonary tuberculosis.
Almost always, a primary infection has no symptoms, but when it does, they are usually imprecise and consist of fatigue and a low-grade temperature without a noticeable cough.
The most common is coughing. Coughing may initially produce very little yellow or green sputum, generally when you get up in the morning, but as the illness worsens, it may produce more. The only cause of hemoptysis is cavitary TB.
Fever, sweats at night, and exhaustion are typical systemic symptoms in people with active tuberculosis.

- Night sweats, sometimes referred to as nocturnal hyperhidrosis, can be strong and moist.
- Low-grade fever
- Fatigue
- Weight loss
- Loss of appetite
- General malaise
- Anorexia

- Dyspnea
- Spontaneous pneumothorax
- Pleural TB with effusion

Diagnosis :-

1) Clinical evaluation
    - Thorough medical history
    - Physical examination
    - Assessment of risk factors for TB infection
    - Disease progression
2) Radiological imaging studies
    - Chest-X ray
    - Computed tomography (CT) scan
3) Microbiological tests
    - Sputum smear microscopy
    - Tissue biopsy samples
    - Nucleic acid amplification tests (NAATs)
    - Acid-fast bacilli (AFB)
    - Tuberculin skin test (TST)
    - Interferon-gamma release assay (IGRAs)
    - Latent TB infection (LTBI)

Treatment :-

I. A component of the best patient case management is directly observed therapy (DOT), which entails public health professionals monitoring the administration of each medication dosage. The probability that the entire treatment course will be finished is increased from 61% to 86% by DOT.

II. Patients who are considered committed to treatment may be eligible for selective self-administered treatment (SAT); ideally, fixed dose combination drug formulations are utilized to prevent the risk of monotherapy, which can result in drug resistance. It has been suggested that mechanical drug monitoring systems can increase SAT adherence.

III. First - line drugs for TB :-
    - Isoniazid (INH)
    - Rifampin (RIF)
    - Pyrazinamide (PZA)
    - Ethambutol (EMB)

IV. Second – line drugs for TB :-
    - Streptomycin
    - Kanamycin
    - Amikacin
    - Capreomycin
    - Fluoroquinolones (Levofloxacin, Moxifloxacin)

V. Other second line drugs :-
    - Ethionamide
    - Cycloserine

- Para-amino salicylic acid (PAS)

VI. Newer anti-TB drugs :-

- Bedaquiline
- Delamanid
- Pretomanid
- Sutezolid

Material :-

First line drugs:

- Isoniazid
- Rifampicin
- Pyrazinamide
- Ethambutol
- Streptomycin

Second line drugs:

Fluoroquinolones:

- Ofloxacin
- Levofloxacin
- Moxifloxacin
- Ciprofloxacin

Other oral drugs:

- Ethionamide
- Prothionamide
- Cycloserine
- Terizidone
- Para-amino salicylic acid (PAS)
- Rifabutin
- Rifapentine

Injectable drugs:

- Kanamycin
- Amikacin
- Capreomycin

1) Isoniazid (INH) :- (Isonicotinic Acid Hydrazide)

It is a first-line drug with excellent efficacy. When mycobacterium tuberculosis is at rest, it is tuberculostatic; when it multiplies quickly, it is tuberculocidal. It is equally effective in acidic and alkaline media and targets both intracellular and external TB .

Mechanism Of Action :-

The main way that INH works is by preventing the synthesis of mycolic acids, which are a special kind of fatty acid found in mycobacterial cell walls. With the aid of the mycobacteria's catalase peroxidase (Kat-G) enzyme, isoniazid, a prodrug, can freely enter the bacteria and transform into an active form (metabolite). This active form inhibits the formation of cell walls and mycolic acid by forming a covalent link with certain enzymes. Bacterial growth is impacted by this.

Pharmacokinetics :-

- INH is fully absorbed orally and permeates all bodily tissues, including the placenta, meninges, and tubercular cavities.
- The liver metabolizes INH, with NAT2's N-acetylation being the primary route.
- Urine is the excretion of the acetylated metabolite.
- There is genetic variation in the rate of INH acetylation:

i. Fast acetylators: 30–40% of Indians have a t1/2 of INH of one hour.
ii. Slow acetylators: 60–70% of Indians have a 3-hour t1/2 of INH.

Adverse Effects :-

1. Peripheral neuritis
2. Hepatitis
3. Neurotoxicity
4. CNS toxicity (psychosis, seizures)
5. Lethargy
6. Rashes
7. Mild anemia
8. Arthralgia

Drug Interaction :-

1. INH absorption is inhibited by aluminum hydroxide.
2. By blocking CYP2C19 and CYP3A4, INH slows the metabolism of phenytoin, carbamazepine, diazepam, theophylline, and warfarin and may increase blood levels of these medications.
3. PAS increases the plasma half-life of INH and suppresses its metabolism.
4. A patient with a G-6 deficiency experiences hemolysis.

Resistance :-

Mycobacterium may become resistant if used alone. It is administered in combination with rifampicin, pyrazinamide, and ethambutol.

2) Rifampicin (R) (RIF) :-

Rifamycin, also known as a sterilizing agent, is a bactericidal drug that works against M-tuberculosis and numerous other gram-positive and gram-negative bacteria. Rifampicin is a semi-synthetic derivative of rifamycin B that is derived from Streptomyces mediterranei. It is safe to use while pregnant.

Mechanism Of Action :-

Rifampicin inhibits bacterial RNA synthesis and influences protein synthesis by binding to the beta-subunit of DNA-dependent RNA polymerase.

Pharmacokinetics :-

• Rifampicin has a 70% bioavailability when taken orally, although absorption is reduced by meals.
• It is extensively dispersed throughout the body, penetrating intracellularly and entering the placenta, tubercular cavities, and caseous masses.
• It undergoes hepatic metabolism to produce an active deacetylated metabolite, which is then eliminated in bile and, to a lesser extent, urine.
• Enterohepatic circulation occurs for rifampicin and its desacetyl derivative.
• Rifampicin has a varied plasma half-life (2–5 hours).

Adverse Effects :-

1. Hepatitis
2. Flushing
3. Pruritus
4. Rash
5. Redness and watering of eyes

Drug Interaction :-

1. Several CYP450 iso-enzymes are increased by rifampicin, a microsomal enzyme inducer.
2. As a result, it improves both its own metabolism and that of numerous medications, such as corticosteroids, sulphonylurease, HIV-Protease Inhibitors, theophylline, metoprolol, fluconazole, ketoconazole, clarithromycin, phenytoin, and oral contraceptives.

Resistance :-

Resistance brought on by RNA polymerase and DNA mutations that alter rifampicin's ability to bind to RNA polymerase.

3) Pyrazinamide (Z) (PZA) :-

Pyrazinamide is chemically related to INH and was created alongside it in 1952. It is tuberculocidal, though weaker than INH and more effective in acidic environments. It is particularly helpful during the first two months of therapy, when inflammatory alterations are noticeable.

Mechanism Of Action :-

The mechanism of action of Z is unknown, although like INH, it is transformed inside the mycobacterial cell into the active metabolite pyrazinoic acid by an enzyme (pyrazinamidase) produced by the pncA gene. This molecule accumulates in acidic environments and likely inhibits mycolic acid synthesis, but by interacting with a different fatty acid synthase than INH. Pyrazinoic acid appears to affect the mycobacterial cell membrane and transport function.

Pharmacokinetics :-

- Pyrazinamide is absorbed orally and is widely distributed and has great penetration in CSF, making it effective in treating meningeal tuberculosis.
- Metabolized in the liver and eliminated in urine.
- Plasma has a half-life of 6-10 hours.

Adverse Effects :-

1. Hepatotoxicity
2. Hyperurecaemia
3. Gout
4. Abdominal destress
5. Arthralgia

Resistance :-

Pyrazinamide resistance develops quickly when administered alone and is mostly caused by mutations in the pncA gene.

4) Ethambutol (E) (EMB) :-

Ethambutol is a synthetic straight-chain molecule that is exclusively tuberculostatic and active against MAC and other mycobacteria, but not other microorganisms. Fast multiplying bacilli are more vulnerable.

Mechanism Of Action :-

Although the exact mechanism of action of E is unknown, it has been discovered to interfere with the incorporation of mycolic acid in the cell wall of mycobacteria by inhibiting arabinosyl transferases (encoded by embAB genes) involved in arabinogalactan production.

Pharmacokinetics :-

- The absorption of an oral dose of E is around ¾.
- It is broadly distributed, but its penetration into menings varies; it has a greater impact in inflammatory conditions.
- It is metabolized in less than half.
- Its plasma half-life is roughly four hours, and it is eliminated in feces and urine through tubular secretion and glomerular filtration.

Adverse Effects :-

1. Loss of visual acuity/ colour vision
2. Retrobulbar neuritis
3. Optic neuritis
4. Peripheral neuritis
5. Hyperurecemia

5) Streptomycin (S) :-

Although it is tuberculocidal and the first clinically successful anti-tubercular medication, it is not as effective as INH or Rifampicin. Due to its low cell penetration, streptomycin exclusively affects extracellular bacilli. Although it enters tubercular cavities, it does not reach the CSF and performs poorly in acidic environments. S is only used as a backup medication or in conjunction with other first-line anti-TB medications. Use is limited to no more than two months. As a result, it is sometimes known as a "supplemental" first-line medication.

Mechanism Of Action :-

Through sporin channels, S enter the bacterial cell wall and reach the periplasmic region attach to the ribosome's 30S subunit. Stop the start of the production of proteins. A protein that is faulty or non-functional is created when the wrong amino acid is incorporated into the expanding peptide chain.

Pharmacokinetics :-

- Because it requires intramuscular injections and has a smaller margin of safety, it is not absorbed orally and does not penetrate the blood-brain barrier.
- It is mostly eliminated via glomerulas filtration, and the dosage should be reduced in the case of kidney failure.

Adverse Effects :-

1. Ototoxicity
2. Nephrotoxicity
3. Myasthenia gravis
4. Teratogenocity

Resistance :-

When S was used alone for tuberculosis, resistance developed quickly, and the majority of patients experienced a recurrence. According to recent studies, S resistance is rising globally. Because of the potential of S-dependency, which occurs when the medicine is prolonged, it is necessary to terminate S-resistant infections as soon as possible. S has no effect on the majority of non-tubercular bacteria.

Method :-

I. In 2023, 48% of TB patients who received their initial test were tested using a WHO-recommended rapid test; 75% of TB patients received treatment; 56% of TB patients with HIV received TPT; and 21% of household contacts received TPT.

Approximately 25% of the world's population is thought to have had TB. After infection, the chance of getting TB disease is at its maximum for the first two years (about 5%), after which it is significantly reduced, and some people will recover from the infection. Approximately 90% of all TB cases that occur each year occur in adults, with a higher incidence among men than women.

Death rates from TB disease are significant (almost 50%) if treatment is not received. Approximately 85% of TB patients can be cured with the current WHO-recommended therapies, which include a course of anti-TB medications for four to six months. Treatment options for TB infections range from one to six months.

Population growth accounts for the majority of the rise in incident instances worldwide between 2022 and 2023. With 134 new cases per 100,000 people, the TB incidence rate in 2023 increased by a negligible 0.2% from 2022.

87% of the world's TB cases in 2023 occurred in 30 high-burden nations, which are home to the majority of those who contract the disease each year.

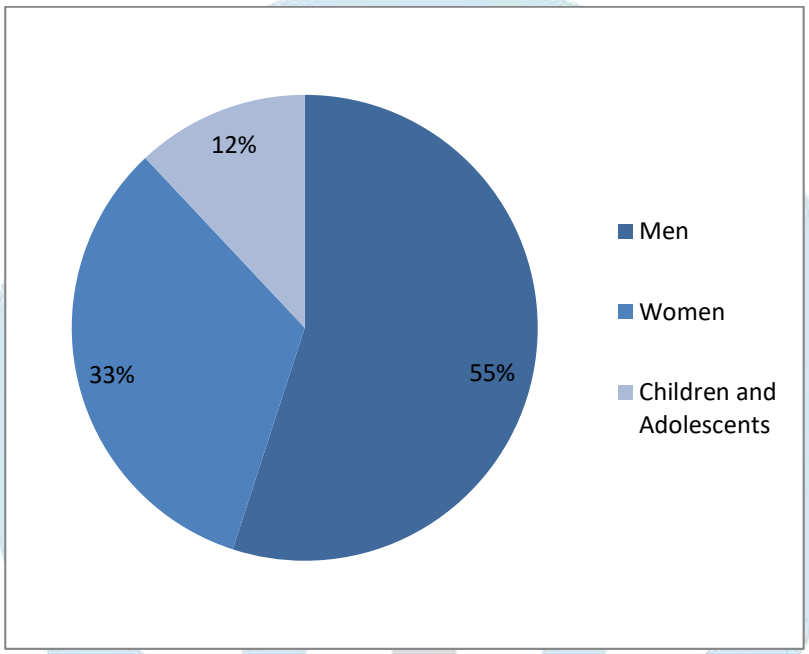
Eight countries accounting for more than two-thirds of the global total:

1. India (26%)
2. Indonesia (10%)
3. China (6.8%)
4. Philippines (6.8%)
5. Pakistan (6.3)
6. Nigeria (4.6%)
7. Bangladesh (3.5%)
8. Democratic Republic of the Congo (3.1%)

56% of the total came from the top five nations.

Estimated number of incident TB cases in 2023 for countries:

1. India – 2 000 000
2. Indonesia – 1 000 000
3. Philippines – 1 000 000
4. China – 1 000 000
5. Pakistan – 1 000 000
6. Bangladesh – 500 000
7. Nigeria – 500 000
8. Democratic Republic of the Congo – 500 000



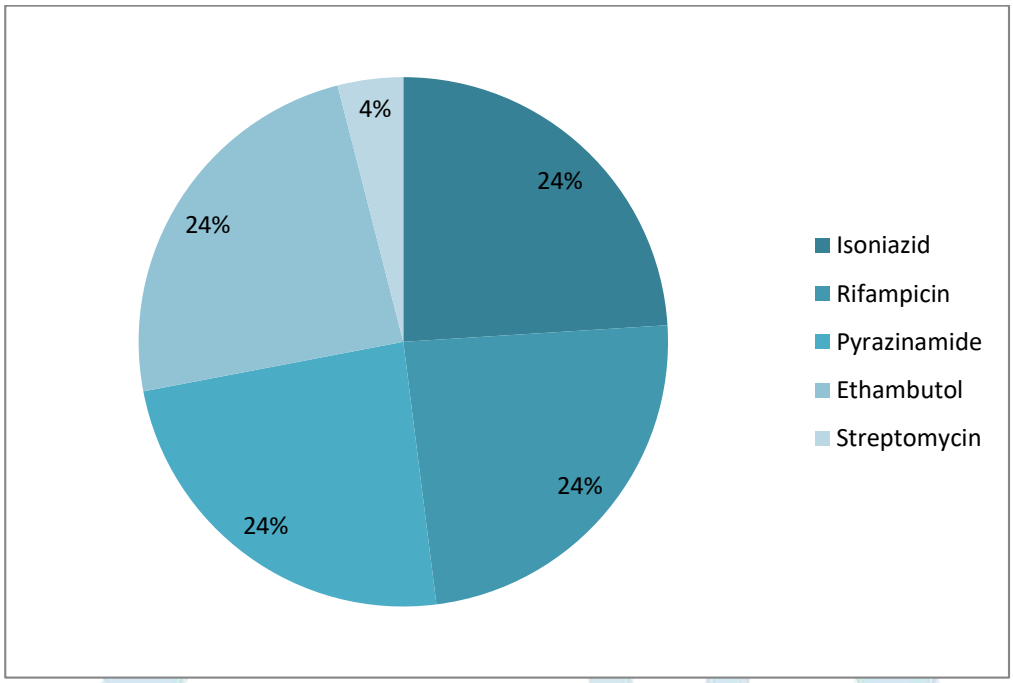
Men accounted for 55% of TB cases in 2023, followed by women (33%), and children and young adolescents (12%).

With an expected 6 million cases in 2023, or 55% of the total, adult males (those over or equal to 15 years) bear the majority of the burden. An estimated 1.3 million instances occurred among children and young adolescents (ages 0–14 years), accounting for 12% of the estimated total, and 3.6 million cases occurred among adult women (aged > over and equal to 15 years), or 33% of the anticipated total.

The greater proportion of TB cases in men is in line with data from national TB prevalence surveys, which indicate that men are more likely than women to contract TB and that there are greater gaps in case detection and reporting among men.

HIV-positive individuals made for 6.1% of all incident TB cases in 2023; this percentage has been gradually dropping for a number of years.

II. Since they are used in combination isoniazid, rifampicin, pyrazinamide, and ethambutol are the most often utilized anti-TB medications.
Up until 2014, streptomycin was administered intramuscularly (IM) as a single dose.



III. Combination of anti-tubercular drugs

For the treatment of TB, the Ministry of Health and Family Welfare of the Government of India primarily recommends two combinations: Initial phase (IP) and Continuous phase (CP), which is a six-month treatment in which IP lasts two months and CP lasts four months.

IP treatment contains:

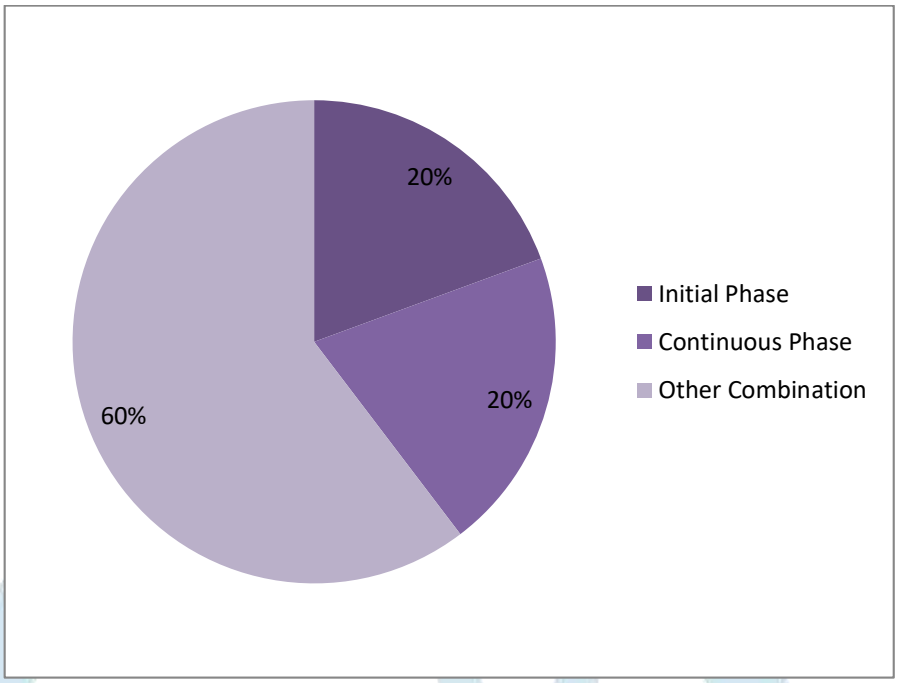
- Isoniazid – 75mg
- Rifampicin – 150mg
- Pyrazinamide – 400mg
- Ethambutol – 275mg

CP treatment contains:

- Isoniazid – 75mg
- Rifampicin – 150mg
- Ethambutol – 275mg

Other combination contains :

- Bedaquiline
- Pretomanid
- Linezolid
- Moxifloxacin
- Rifapentine



IV. Safety and Efficacy :-

Drugs	Concentration Range	Proportions of Drugs
Isoniazid	0.2 – 15 mg/liter	70%
Rifampicin	0.3 – 25 mg/liter	110%
Pyrazinamide	0.2 – 70 mg/liter	95%
Ethambutol	0.1 – 10 mg/liter	90%

Summary of pharmacokinetic measures of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol

Drugs and Parameters	2-h level (mg/liter)	Tmax (h)	Cmax (mg/liter)	t1/2 (h)	AUC0-8 (mg/liter)
Isoniazid					
Median	5.4	2	6.7	2.9	25.9
Interquartile range	3.7 – 7.2	1.2 – 2.7	5-8.5	2.2 – 3.6	18.8 – 32.9
Rifampicin					
Median	4.4	2.6	6.5	2.1	23.3
Interquartile range	2.2 – 6.6	2.1 – 3.2	4.4 – 8.6	1.6 – 2.7	15.2 – 31.5
Pyrazinamide					
Median	48.9	1.6	53.7	6	288.5
Interquartile range	41.2 – 56.7	1.0 - 2.3	46.1 – 61.5	4.8 – 7.2	245.9 – 335.5
Ethambutol					
Median	3.4	2.7	5.2	2.6	20.3
Interquartile range	2.3 – 4.6	2.1 – 3.5	4.2 – 6.4	2.2 – 3.2	16.4 – 24.3

V. Drugs used in treatment of TB during pregnancy :-

The World Health Organization (www.who.int) and the International Union Against Tuberculosis and Lung Disease (www.theunion.org) support for pregnant women with TB to follow regular first-line medication regimens. In pregnant women with tuberculosis, this guideline supports the use of the usual first-line medications isoniazid, rifampicin, ethambutol, and pyrazinamide. These TB medications are not contraindicated during pregnancy since they have not been demonstrated to have teratogenic effects, despite the fact that they cross the placenta.

INH, RIF, and EMB daily for two months, followed by INH and RIF daily or twice weekly for seven months (for a total of nine months of treatment) is the recommended initial treatment regimen.

i. Isoniazid: Isoniazid is thought to be safe to take while pregnant, however in order to avoid neuropathy, pyridoxine supplementation is necessary.
Although it is eliminated in breast milk, breastfeeding infants are not at serious risk from it (10). Women who are nursing and taking INH should additionally take supplements of pyridoxine (vitamin B6).

ii. Rifampicin: Very little information is available regarding the hazards to the fetus after rifampicin exposure during pregnancy. Exposure to rifampicin has not been linked to an increased risk of miscarriage, congenital deformity, preterm delivery, or low birth weight. When rifampicin is given in the weeks before delivery, it is advised that the mother take vitamin K supplements and that the newborn receive intramuscular vitamin K at birth because there have been reports of neonatal hemorrhage after exposure to rifampicin in late pregnancy.

iii. Ethambutol: This medication can be used during pregnancy without the need for special safety measures. Due to concerns about eye toxicity and the availability of better treatment options, its use in high therapeutic dosages in neonates and infants is generally avoided; however, its use during pregnancy is not advised.

iv. Pyrazinamide: During pregnancy, pyrazinamide administration is advised. Despite the lack of animal or epidemiological studies, pyrazinamide has not been linked to any reports of prenatal abnormalities. The United States Centers for Disease Control and Prevention (CDC) guidelines still do not recommend the use of pyrazinamide during pregnancy due to the lack of such data. Nonetheless, this guideline recommends its usage and is supported by other TB authority, including as the World Health Organization and the International Union Against Tuberculosis and Lung Disease. In the absence of pyrazinamide, a 9-month course of isoniazid and rifampicin is advised, with ethambutol added until data on drug susceptibility are obtained. Because of the increased risk of hepatotoxicity, pyrazinamide treatment during pregnancy necessitates intensive clinical observation and increased monitoring of liver function tests at least monthly.

v. Streptomycin: Due to evidence of adverse effects on the fetus, streptomycin is contraindicated during pregnancy.

VI. TB and HIV Co-Infection Control:

6.1% of persons in 2023 were HIV positive; this percentage has been gradually dropping over the past few years.

Co-trimoxazole therapy and **anti-retroviral therapy (ART therapy)**, are frequently used to treat this infection.

Result and Discussion :-

As we observed, it is estimated that about 25% of people worldwide have experienced tuberculosis. The current WHO-recommended therapy, which include a course of anti-TB drugs for four to six months, can cure about 85% of TB patients. With 2,000,000 incident TB cases in 2023, India has the highest percentage ratio of any country in the world (26%).
Men account for a higher percentage of TB cases than women, children, and young adolescents. 55% of cases in 2023 were male (6 million cases), 33% were female (3.6 million cases) and 12% were children and young adolescents (1.3 million cases).

More widely used anti-TB drugs than streptomycin in our comparative analysis include isoniazid, rifampicin, pyrazinamide, and ethambutol. India suggests two treatment options for tuberculosis (TB): Initial Phase (IP) and Continuous Phase (CP), both of which are six-month treatments with IP lasting two months and CP lasting four months. Treatment for IP includes:

75 mg of isoniazid, 150 mg of rifampicin, 400 mg of pyrazinamide, and 275 mg of ethambutol. Treatment for CP includes:

75 mg of isoniazid, 150 mg of rifampicin, and 275 mg of ethambutol.

Isoniazid, rifampicin, pyrazinamide, and ethambutol have pharmacokinetic measures of 5.4 mg/liter, 4.4 mg/liter, 48.9 mg/liter, and 3.4 mg/liter, respectively, at the 2-hour level.
The corresponding Tmax values are 2, 2.6, 1.6, and 2.7.
The corresponding Cmax values are 6.7 mg/liter, 6.5 mg/liter, 53.7 mg/liter, and 5.2 mg/liter.
The corresponding AUC0-8 are 25.9 mg/liter, 23.3 mg/liter, 288.5 mg/liter, and 20.3 mg/liter.
According to this study, pyrazinamide has the highest 2-hour level and ethambutol has the lowest; ethambutol has the highest Tmax value and pyrazinamide has the lowest Tmax value; pyrazinamide has the highest Cmax value and ethambutol has the lowest Cmax value; and pyrazinamide has the highest AUC0-8 and ethambutol has the lowest AUC0-8.
Because of its consistent values, we found that Rifampicin is a safer and more effective medication.

The WHO and the International Union Against Tuberculosis and Lung Disease advise pregnant women with TB to take INH, RIF, PZA, and EMB as first-line treatment regimens. INH, RIF, and EMB every day for two months, then INH and RIF every day or every two weeks for seven months.

DRUGS	PREFERRED OR NOT
Isoniazid	Preferred
Rifampicin	Preferred
Pyrazinamide	Not Preferred
Ethambutol	Not Preferred
Streptomycin	Not Preferred

In 2023, 6.1% of persons had both HIV and TB, however this percentage has been steadily declining in recent years. This infection is commonly treated with co-trimoxazole medication and anti-retroviral therapy (ART therapy).

Conclusion :-

We concluded from this study that, in comparison to other nations, India has the highest percentage ratio for TB. Men are more likely than women or children and adolescents to have tuberculosis. According to these comparative studies, the most potent and well-tolerated oral medications include isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. These first-line treatment regimens are also more effective and less toxic than second-line drug regimens. Streptomycin is contraindicated during pregnancy, while rifampicin is a safer and more effective medication than

others.

When HIV and TB co-infect Anti-retroviral therapy (ART) and co-trimoxazole therapy are usually used.

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