PHARMACOVIGILANCE - POST MARKETING SURVEILLANCE NEWS

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Editor's Note

We wish to thank all our numerous stakeholders who have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to sending out quarterly newsletter to its stakeholders. The objectives of the Newsletter are to disseminate information on Pharmacovigilance activities nationally and globally, to educate stakeholders on medicine safety issues, to promote rational use of drugs and to promote spontaneous reporting. This first quarter newsletter focuses on Pharmacovigilance of anti-tuberculosis drugs. Other features in this edition include compilation of adverse reactions as documented in Reactions' Weekly.

We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions. Your valued comments and acknowledgement of receipt of this issue through our email addresses (nafdac_npc@yahoo.com; pharmacovigilance@nafdac.gov.ng) would be most appreciated.

Have a most blessed 2014!

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*Text any DRUG RELATED PROBLEM to the **SHORT CODE 20543 (**For **free** on **MTN, Glo and Etisalat)** for action by the Pharmacovigilance Centre*

OVERVIEW OF TUBERCULOSIS INFECTION AND DISEASE

Tuberculosis (TB) is a bacterial infection caused by the Mycobacterium tuberculosis complex especially *Mycobacterium tuberculosis.* It affects mainly the lungs but may also spread to other organs. The hallmarks of active TB infection are a chronic cough (with blood-tinged sputum), fever, night sweats, and weight loss. People at high risk of TB infection include individuals likely to be exposed to TB infection such as close contacts of TB patients, people who reside or work in high risk settings as well as in TB endemic areas amongst others. Furthermore, some people are more likely to be infected by the TB bacteria on exposure. The likelihood of infection and progression to active disease is augmented by conditions and factors that impair the immune system. These include HIV/AIDS, silicosis, malnutrition, diabetes, long term steroid use, tobacco use, alcoholism, crowding, end stage renal disease and very young age(<5 years old).[1]

Tuberculosis is one of the most common infectious diseases in the world. According to data from WHO, approximately one third of the world's population is living with latent or inactive tuberculosis. Of these, 1 in 10 will develop an active, infectious and symptomatic disease over a lifetime period. The chances of developing active disease may however be exacerbated in persons with conditions that weaken their immunity; HIV infected persons being 30 times more likely to develop active disease compared to people without HIV. A person with active TB can infect 10 to 15 other people every year and if left untreated, more than 50% of active TB cases will result in mortality. Hence, active as well as latent cases of TB infection need to be adequately treated. WHO recommends a standard treatment for active, drug-sensitive tuberculosis comprising a supervised 6-month course of four antimicrobial drugs[2]. On the other hand, in the treatment of Latent TB, a single antibiotic is generally employed.[3]

Although, TB is a global public health concern, it predominantly affects people in resource poor settings mostly in Africa and Asia. Nigeria is one of the 22 high burden TB countries in the world with an estimate of 210,000 new cases of all forms of TB in 2010 equivalent to 133/100 000 population. Conversely, the mortality rate declined from 11% in 2006 to 5% in 2010 attributable to treatment success. The nation has expanded the Directly Observed Treatment Short-course (DOTS) centres, amplified TB laboratory services, and established more community TB care activities in its efforts to tackle the TB problem. However, there is still a great deal to be done in order to meet the

nations' TB program under the stop TB partnership, which is to halve the TB prevalence and mortality rates by 2015 compared with 1990 levels.[4] The Sop TB partnership has their global TB control efforts undermined by the emergence of multiple-drug resistant tuberculosis (MDR-TB)[5] and increase in HIV-associated tuberculosis[6]. These also pose a challenge to the achievement of some of their goals by the deadline of 2015.

MULTIPLE-DRUG RESISTANT TB (MDR-TB)

MDR-TB can be defined as resistance to the two most effective first-line TB drugs namely Rifampicin and Isoniazid. Progressing from MDR-TB, extensively drug-resistant TB (XDR-TB) has additional resistance to any of the fluoroquinolones and at least one of three injectable second-line drugs which include amikacin, kanamycin, or capreomycin[7]. As of 2013, 3.7% of new tuberculosis cases and 20% of previously treated cases have MDR-TB.[8]

A person may be primarily infected with a resistant strain of TB or one with fully sensitive TB may develop secondary (acquired) resistance during therapy; attributable to inadequate treatment, lack of adherence, or use of low-quality medication. Secondary resistance is of higher public health significance, and the weight of its prevention rests on all stakeholders; the healthcare providers, the patients and medicine regulators. This is given that a secure and uninterrupted drug supply is maintained by the public health programs. Also, the laboratory has the responsibility to detect drug resistance as soon as possible to enable the clinician design an effective multi-drug regimen hence preventing bacterial selection and further acquisition of drug resistance.[9]

Treatment of MDR-TB is cumbersome and can take up to two years of multi-drug regimen. Similarly, there are limited treatment options for MDR-TB, therefore the use of second-line drugs are employed. These however are less effective, more expensive and toxic. Additionally, the treatment outcome is significantly poorer in MDR TB and XDR TB.[10,8] The occurrence of serious adverse events with these drugs further impedes adherence to the treatment regimen making room for development of even more resistance. All cases of adverse events and quality issues with the drugs should be reported to the NPC for necessary actions to be executed.

The U.S. Food and Drug Administration (FDA) in December 2012 approved a new drug to treat MDR-TB, Bedaquiline. It is to be used in combination therapy for patients who have failed standard treatment and have no alternative options.[11]

HIV/AIDS ASSOCIATED TB

High HIV prevalence rates have been associated with rising tuberculosis case notifications, disproportionally more patients with smear-negative disease, high case fatality, high rates of tuberculosis recurrence, drug-related side-effects, and outbreaks of MDR TB and XDR TB. At the same time, tuberculosis is recognized in HIV programmes as one of the most common causes of morbidity and the leading cause of mortality accounting for approximately one quarter of global HIV/AIDS deaths. TB and HIV are a fatal combination; each aids the progression of the other. The high TB burden in some nations like South Africa is attributable to a concomitant high HIV prevalence in those nations available global data suggests that new TB cases would be on the decline but for HIV prevalence[12].

Co-infection with HIV complicates TB diagnosis, reducing the accuracy of both Sputum smear microscopy and radiography. TB presentations are often atypical in people with advanced HIV-related immune-deficiency; the disease may also be extra-pulmonary and disseminated. Although HIV-positive patients with smear-negative TB are apparently less infectious than smear-positive cases, they have more adverse drug reactions, and suffer higher mortality rates on treatment. The treatment of TB and HIV co-infected patients requires antituberculosis and antiretroviral drugs to be administered concomitantly. The challenges here include pill burden and patient compliance, drug interactions, overlapping toxic effects, and immune reconstitution inflammatory syndrome[13].

The increasing prevalence of HIV associated TB has challenged the directly observed therapy short course as the sole tuberculosis control system necessitating effective collaborative HIV and TB services. Early HIV testing and start of ART is advocated for tuberculosis prevention and intensified TB case finding, infection control, and isoniazid preventive therapy to reduce HIV-related tuberculosis morbidity and mortality. [14]

ADVERSE DRUG REACTIONS IN TUBERCULOSIS AND MULTI DRUG RESISTANT TUBERCULOSIS (REPORT FROM THE NPC DATABASE)

Standard treatment of tuberculosis and multi-drug resistant tuberculosis (MDRTB) pose difficulties in treatment and often results in increased frequency of adverse reactions to anti-tuberculosis drugs (ADRAs) leading to complications in co-infected patients with HIV and other co-morbidities. A total of 209 patients placed on anti-tuberculosis agents that developed adverse drug events were reported to the National Pharmacovigilance Centre (NPC) from 2004 to February 2014 and these reports were retrospectively studied and analysed.

Majority of the patients, 183 had multidrug resistant tuberculosis and were placed on second line antituberculosis drugs. The drugs include prothionamide, kanamycin, cycloserin, levofloxacin, amikacin and ethionamide while an incomplete withdrawal of some first line drugs, especially pyrazinamide was reported in some patients. Twenty six (26) patients were however on standard treatment (first line antituberculosis drugs) and these include rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin. The most common anti TB drug combinations reportedly prescribed were Prothionamide, Pyrazinamide, Cycloserine, Kanamycin, Levofloxacin(42% of 183), Prothionamide, Cycloserine, Kanamycin, Levofloxacin(12.6% of 183), Prothionamide, Pyrazinamide, Cycloserine, Levofloxacin(9.3% of 183) for MDR-TB (Table1.1); and Pyrazinamide, Rifampicin, Isoniazid, Ethambutol(19.2% of 26), Pyrazinamide, Ethambutol, Rifampicin(15.4% of 26) for susceptible TB. (Table1.2). Three (3) MDR-TB patients and 1 standard TB patient were reportedly also receiving antiretroviral therapy. It is likely that more of the patients either had undiagnosed HIV or were not yet on antiretroviral therapy.

The proportion of severe reactions and the emergence of ADRs in both groups differ greatly. Also, there were differences in the type of reactions between the two groups with a higher frequency in MDR-TB patients than patients on standard treatment. Majority of the MDR-TB patients developed neurological complications including psychosis, depression, vertigo, dizziness, and headache; gastrointestinal disorders, peripheral neuropathy, urticaria, ear and labyrinth disorders such as tinnitus and hearing loss (Table 1.3). However, patients on standard treatment (first line antituberculosis drugs) experienced gastrointestinal disorders, vestibular disorders, skin and subcutaneous tissue disorders. The reactions seen with the anti- tuberculosis drugs are in line with the global trends especially with the second line drugs used in MDR-TB.

Table 1.1 MDR-TB drug regimens and associated ADRs as reported

S/N	DRUG REGIMEN	CONCOMITANT DRUGS	ADRS
1	PROTHIONAMIDE, PYRAZINAMIDE, CYCLOSERINE,KANAMYCIN, LEVOFLOXACIN(78)	PYRIDOXINE(49) PYRIDOXINE, HAEMATINICS(4) EFV, 3TC,AZT,HAEMATINICS(1)	PSYCHOSIS(12), DEPRESSION(7), ANXIETY(2), MEMORY DEFFICIT(1) NEUROLOGICAL COMPLICATIONS(9), SEIZURES(2), DIZZINESS(3) VESTIBULAR SYMPTOMS(11)LOSS OF HEARING(9), VERTIGO(4), TINNITUS(5), ARTHRITIC SYMPTOMS(1), ARTHRALGIA(7), SLEEP DISTURBANCE(11), GASTRITIS(4), DIARRHOEA(4), ABDOMINAL PAIN(2), DYSPEPSIA, URTICARIA(5), SKIN REATION, OEDEMA(2), FUNGI INFECTION(3), VAGINAL CANDIDIASIS(3), NON SPECIFIC PAIN(6), MUSCULOSKELETAL PAIN, ANAEMIA, HEPATOTOXICITY, VOMITING(13), NAUSEA(3), NASAL CONGESTION(2),
2	PROTHIONAMIDE, CYCLOSERINE,KANAMYCIN , LEVOFLOXACIN(23)	PYRIDOXINE(1)	PSYCHOSIS(2), DEPRESSION(3), LOSS OF HEARING(9), TINNITUS(1) CARDIOVASCULAR SYMPTOMS(HEART FAILURE, HYPERTENTION, URINE RETENTION, OEDEMA), NEUROLOGICAL COMPLICATIONS(1) NUMBNESS IN HANDS(1), TARDIVE DYSKINESIA, SLEEP DISTURBANCES(3), DYSPNOEA, NAUSEA/ VOMITING(3), PRURITUS
3	PROTHIONAMIDE, PYRAZINAMIDE, CYCLOSERINE(17), LEVOFLOXACIN	PYRIDOXINE(2)	PSYCHOSIS(4), DEPRESSION(4)GASTRITIS(1), GIT UPSET(2), SLEEP DISTURBANCE(5), DROWSINESS(1), CHEST PAIN, BODY PAIN(4), JOINT PAIN(2) ELECTROLYTE IMBALANCE, HEADACHE(2), MACROGLOSSIA, FUNGI

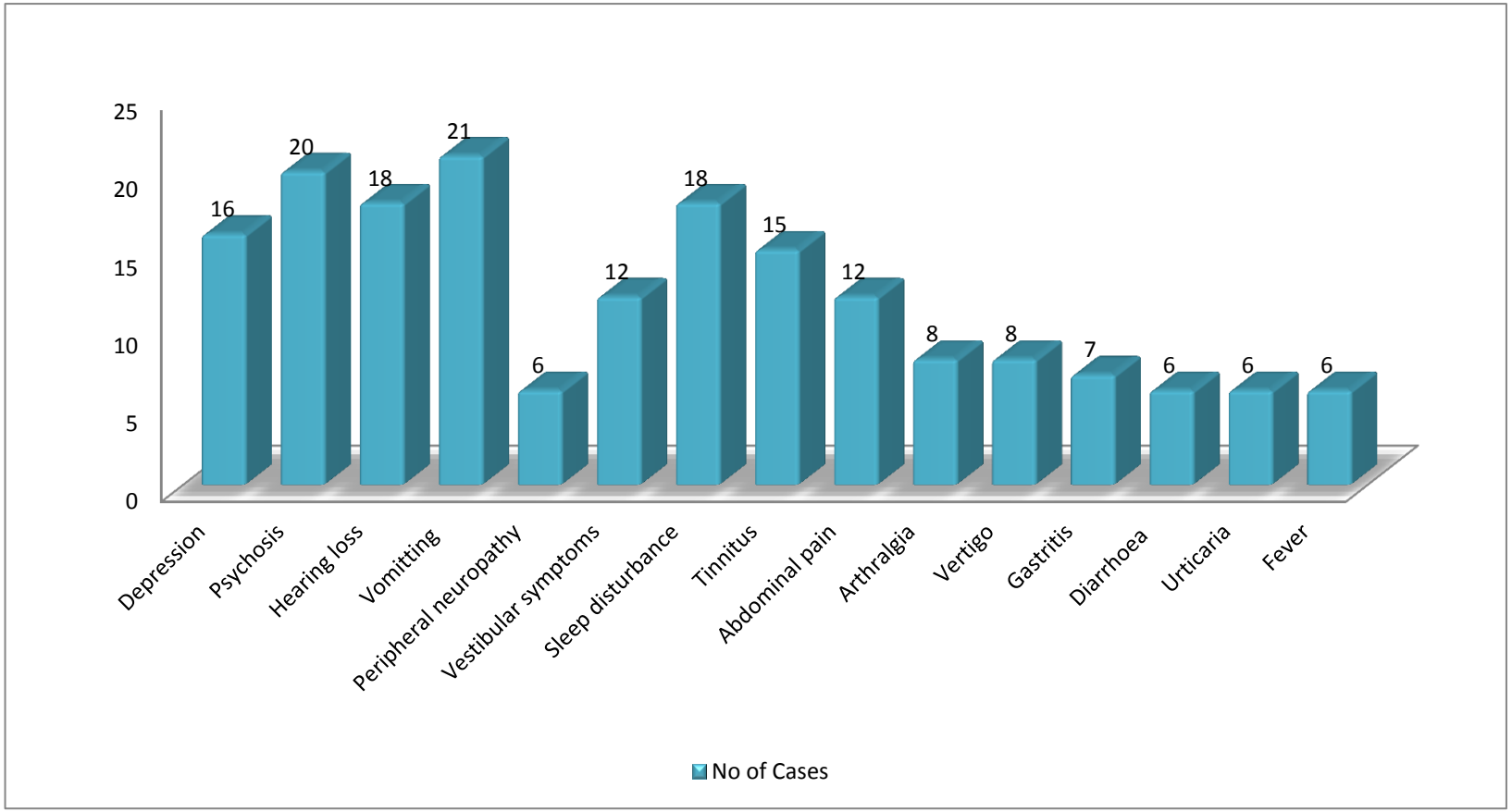
			INFECTION, WEAKNESS, PARAGEUSIA(3), ANOREXIA, PRURITUS, OEDEMA
4	PROTHIONAMIDE, CYCLOSERINE, LEVOFLOXACIN(8)		PSYCHOSIS, RESTLESSNESS, HEADACHE(4), FEVER(2), ABDOMINAL PAIN(2) GASTRITIS(2), ANOREXIA(3), VOMITTING, BODY PAIN(2), WEAKNESS(2) PRURITUS
5	PROTHIONAMIDE, PYRAZINAMIDE, LEVOFLOXACIN(7)	PYRIDOXINE(1)	NEUROLOGICAL COMPLICATIONS, PALPITATIONS, PALLOR ELECTROLYTE IMBALANCE, HEADACHE, TINNITUS, BODY PAINS(2), JOINT PAINS, GASTRITIS(1) ABDOMINAL PAIN(1) VOMITING, PRURITUS(2), PATCHES ON SKIN(1),
6	PROTHIONAMIDE, CYCLOSERINE,KANAMYCIN(1),	ARV(1)	TINNITUS(1)
7	PROTHIONAMIDE, PYRAZINAMIDE, CYCLOSERINE, KANAMYCIN(7)	PYRIDOXINE(1) PYRIDOXINE, HAEMATINICS(2)	PSYCHOSIS(1), DEPRESSION(2), VESTIBULAR SYMPTOMS, NEUROLOGICAL COMPLICATION, PERIPHERAL NEUROPATHY, SLEEP DISTURBANCE, URTICARIA, INJECTION SITE ATROPHY, EPIGASTRIC PAIN
8	PROTHIONAMIDE, PYRAZINAMIDE, KANAMYCIN, LEVOFLOXACIN(5)	PYRIDOXINE(1)	VOMITING,ABDOMINAL DISCOMFORT(3), PRURITUS
9	PROTHIONAMIDE, PYRAZINAMIDE, KANAMYCIN(1)		WEAKNESS
10	PYRAZINAMIDE, CYCLOSERINE, LEVOFLOXACIN(3)		HEADACHE(3), MACROGLOSSIA, INJECTION SITE ATROPHY, BODY PAIN, ARTHRALGIA, WEAKNESS
11	CYCLOSERINE,KANAMYCIN, LEVOFLOXACIN(2)		HEADACHE(2), FEVER(2)
12	PROTHIONAMIDE, PYRAZINAMIDE, CYCLOSERINE(2)		GIT DISTURBANCE, FEVER, HEADACHE, BODY PAIN(2), HEADACHE,WEAKNESS
13	PROTHIONAMIDE, PYRAZINAMIDE, LEVOFLOXACIN, CYCLOSERINE, AMIKACIN(5)	PYRIDOXINE(4)	DIZZINESS, DROWSINESS, MALAISE, CHEST PAIN, JOINT PAIN,DIARRHOEA(2),VOMITING, PYROSIS, DIZZINESS, PRURITUS
14	PYRAZINAMIDE, CYCLOSERINE, LEVOFLOXACIN, AMIKACIN (1)		HEARING IMPAIRMENT, JOINT PAIN AND SWELLING, LEG BLISTERS
15	PROTHIONAMIDE, LEVOFLOXACIN, CYCLOSERINE, KANAMYCIN		VESTIBULAR SYMPTOMS, JOINT PAIN

	AMIKACIN(1)		
16	CYCLOSERINE, FLUOROQUINOLONE(not specified) KANAMYCIN, (1)		DYSPEPSIA
17	CYCLOSERINE, KANAMYCIN, FLUOROQUINOLONE, (not specified) ETHIONAMIDE(1)		DYSPEPSIA, PRURITUS
18	STREPTOMYCIN, ISONIAZID, CYCLOSERINE(2)		BLURRED VISION, PARASTHESIA, NUMBNESS
19	KANAMYCIN(3)		VESTIBULAR SYMPTOMS(2), FASICULATION
20	PROTHIONAMIDE, PYRAZINAMIDE, CYCLOSERINE FLUOROQUINOLONE(not specified),KANAMYCIN(1)		MYALGIA
21	PYRAZINAMIDE(2)		HEADACHE, RESTLESSNESS, FEVER, RASHES, PRURITUS
22	CYCLOSERINE(6)		MOOD DISORDER, PERIPHERAL NEUROPATHY(2)
23	CYCLOSERINE,KANAMYCIN, LEVOFLOXACIN, PYRAZINAMIDE(2)		SLEEP DISTURBANCE, HEADACHE, INJECTION SITE ATROPHY, TENDONITIS, ARTHRALGIA
24	LEVOFLOXACIN(3)		INSOMNIA, FUNGI INFECTION, PEDAL OEDEMA/ PAIN, JOINT PAIN
25	PROTHIONAMIDE(1)		HEADACHE, ABDOMINAL PAIN

Table 1.2 First line TB drug regimens and ADRs as reported

S/N	TB DRUG REGIMEN	CONCOMITANT MEDICATIONS	ADVERSE EVENTS
1	PYRAZINAMIDE, RIFAMPICIN, ISONIAZID, ETHAMBUTOL(5)	CODEINE(1), TRAMADOL(1), PREDNISOLONE(1)	FULMINANT HEPATITIS,RESPIRATORY DISTRESS, ANGIO OEDEMA, SEIZURES, STEVEN JOHNSON'S SYNDROME, URTICARIA
2	RIFAMPICIN, CIPROFLOXACIN		STEVEN JOHNSON'S SYNDROME
3	PYRAZINAMIDE, ETHAMBUTOL, RIFAMPICIN(4)	PYRIDOXINE(1)	JAUNDICE, DERANGED LIVER ENZYMES, WHITE PATCHES ON SKIN, NUMBNESS OF FEET, CONSTIPATION
4	RIFAMPICIN(2)	EFV, 3TC(1)	LOSS OF VISION, URTICARIA, DARKENING OF SKIN
5	ISONIAZID		ABDOMINAL DISCOMFORT, VOMITING, WEAKNESS
6	ETHAMBUTOL(2)	TDF,3TC,NVP,COTRIM(1)	LOSS OF VISION, BLURRED VISION, COLOURATION OF EYES
7	ISONIAZID, ETHAMBUTOL		URTICARIA, ORAL THRUSH
8	ETHAMBUTOL, PYRAZINAMIDE		ITCHY EYE RESULTING TO WHITISH GROWTH
9	ISONIAZID, RIFAMPICIN(2)	PYRIDOXINE	URTICARIA, NAUSEA/VOMITING
10	OFLAXACIN		WEAKNESS, RESTLESSNESS, DIZZINESS
11	CEFTAZIDIME, PYRAZINAMIDE, RIFAMPICIN	QUININE	FOCAL SEIZURES, RIGORS, VOMITING,HIGH TEMPERATURE
12	CEFTRIAZONE, STREPTOMYCIN		RASHES
13	ETHAMBUTOL, RIFAMPICIN	COTRIMOXAZOLE, MULTIVITAMINS	PRURITUS, WEAKNESS
14	ISONIAZID, PYRAZINAMIDE, ETHAMBUTOL	GLIBENCLAMIDE	RASHES, ABDOMINAL DISCOMFORT
15	STREPTOMYCIN		VESTIBULAR AND AUDITORY DAMAGE

Table 1.2 Adverse drug reactions in multi-drug resistance tuberculosis



Source: Generated from the NPC database

Adverse Drug Reaction to Antituberculosis drugs (ADRAs) could be viewed as an important cause of long term morbidity and influences adherence to prescribed medicines sometimes necessitating the use of ancillary medication or the suspension of treatment.

ADVERSE DRUG REACTIONS CULLED FROM THE REACTIONS' WEEKLY

Rifampicin/isoniazid/Pyrazinamide

Allergic reaction: case report
An 83-year-old man developed an allergic reaction following administration of rifampicin/isoniazid/pyrazinamide [Rifater). Pyrazinamide and rifampicin were assumed to be causative, following subsequent investigations.

The man had a pacemaker, and a history of hypertension and asthma. He began receiving rifampicin/isoniazid/pyrazinamide and ethambutol for bacilliferous tuberculosis *[dosages not stated].* On the fourth day, he developed a skin eruption on his lower limbs, and discontinued treatment; he was hospitalised to restart treatment. On day 1, he received isoniazid 5 mg/kg/day without any reaction. Ethambutol 20 mg/kg/day was added the following day without clinical manifestations; similarly, he appeared to experience no reaction after receiving rifampicin 8 mg/kg/day. However, severe bronchospasm developed on day 4 (without skin eruption) 1 hour after the addition of pyrazinamide (three tablets *[dosage not stated)).* Pyrazinamide was suspected to have caused the bronchospasm, and was not given again. On day 5, he received the three other antibiotics at approximately 8 o'clock. Two hours later, he experienced an anaphylactic reaction including generalised erythema, severe pruritus, sinus tachycardia, severe bronchospasm and a high BP.

The man received oxygen, a calcium antagonist, salbutamol [albuterol]and corticosteroids. His bronchospasm improved, his BP reduced and his erythema gradually resolved. A hypersensitivity reaction to one of the three antibiotics was suspected. Subsequent intradermal testing was strongly positive with rifampicin, producing an immediate reaction similar to the one before (bronchospasm and generalised pruritus) despite continued corticosteroid therapy. His condition improved following salbutamol and antihistamine administration. He subsequently underwent successful induction of immunotolerance to rifampicin, reaching the effective dose of 600mg on day 5; isoniazid then ethambutol was subsequently restarted. The three antibiotics were continued without problems, for approximately 2 weeks, until retrobulbar optic neuritis was observed. Ethambutol was

subsequently switched to a fluoroquinolone; corticosteroids were gradually discontinued. At last follow up, he was well and continuing dual therapy with isoniazid plus rifampicin.
Author comment: *[Sloth pyrazinamide and rifampicin were assumed to be the causative agents, despite* a *negative skin prick test for pyrazinamide, but the skin test for rifampicin was confirmed positive.*

Lafourcade M-P. et al. Allergic reactions to antituberculosis drugs. Revue Francaise d' Allergologie 49: 496-499, No.6. Oct 2009 [French: summarised from a translation] - France SOt158183

Antituberculars/antiretrovirals

Hepatitis and death: case report

A 54-year-old man developed drug-induced hepatitis during treatment with isoniazid, rifampicin, ethambutol and pyrazinamide. Following resolution of his tuberculosis (TB), he began antiretroviral therapy with tenofovir*, emtricitabine and efavirenz, and subsequently died. *[No dosage information stated].*
The man presented with fever, cough, dysphagia and weight loss. He had TB, and an HIV viral load of > 500 000 copies/mL. He began antituberculosis therapy with isoniazid, rifampicin, ethambutol and pyrazinamide administered through a jejunostomy tube. Two weeks later, he developed hepatitis (AST 470 U/L, ALT 304 U/L).
Isoniazid, rifampicin and pyrazinamide were withdrawn; however, the man continued ethambutol, and began receiving the second-line agents: levofloxacin and streptomycin. His liver enzymes normalised, and rifampicin was reintroduced. His AST and ALT levels once again increased, and rifampicin was ceased. Isoniazid was then reintroduced, and was tolerated well. His condition improved and streptomycin was discontinued. He achieved clinical resolution of his TB infection; however, he remained severely debilitated from his advanced AIDS. He began receiving tenofovir, emtricitabine and efavirenz. He became febrile and hypotensive 4 days later but refused further evaluation or intervention. He died a few days later; death was attributed to possible antiretroviral drug toxicity or immune reconstitution syndrome.

* It was not specified whether this patient was receiving tenofovir or tenofovir disoproxil fumarate

Rapose A, et al. Esophageal perforation and pneumomediastinum: rare complications of tuberculosis. Infectious Diseases in Clinical Practice 16: 266-267, No.4, Jul 2008 - USA 801150146

Ethambutol/isoniazid/rifampicin
Liver injury: case report

A 40-year-old woman was diagnosed with renal tuberculosis and started receiving rifampicin 600 mg/day, ethambutol 800 mg/day and isoniazid 150 mg/day; she had received one course of nitrofurantoin 5 months earlier. After 3 weeks, her fever subsided. However, after 2 months' treatment, she developed severe liver injury with ALT and AST levels of 179 and 198 U/L, respectively. Antituberculars were discontinued and she received an oral Chinese herbal concoction for her tuberculosis. Her transaminase levels then normalised and, after 12 months,
she had recovered completely. .

Tong Y, et al. A renal tuberculosis case: could Chinese medicine play a role? Journal of Alternative and Complementary Medicine 15: 939-941. No.8, I Aug 2009 - China 801158331

Rifampicin

Addison's disease in an elderly patient: case report
An 82-year-old woman developed Addison's disease during treatment with rifampicin.
The woman was hospitalised in January 2002 with miliary tuberculosis and started receiving rifampicin 450 mg/day, isoniazid and ethambutol; at this time, her weight was 45.3kg and her height was 133cm. A few days after treatment initiation, her overall condition had deteriorated and she had developed a worsening general malaise, appetite loss and vomiting. Seven days after rifampicin initiation, she had developed hyponatraemia (125 mEq/L), hypochloraemia (89 mEq/L) and hyperkalaemia (5.6 mEq/L). She had a decreased level of 24-hour urinary ketosteroid (2.4 mg/day), an increased level of rennin activity (6.2mg/mL/h) and an increased level of adrenocorticotrophic hormone (ACTH; 440 pg/mL) in her plasma. Nine days after treatment initiation, she had
Lost 2.9kg of body weight, but her fever had subsided.
Rifampicin was discontinued and the woman started receiving streptomycin; isoniazid and ethambutol were continued. She also received saline for hyponatraemia. Her general malaise greatly improved. An abdominal CT scan

showed a swelling of her right adrenal gland. She was diagnosed with tubercular Addison's disease and the adrenal crisis induced by rifampicin. Her adrenal gland insufficiency showed gradual improvement. However, a CT scan of her right adrenal gland was suggestive of necrosis inside the gland. Her hyponatraemia normalized and an ACTH test showed up regulation of the cortisol level. Rifampicin 150 mg/day was restarted and the woman exhibited no symptoms of adrenal crisis. Her adrenal function was still insufficient, but she was asymptomatic. She was discharged 4 months after admission. At 1 year and 4 months after the initial presentation, her adrenal gland was still swollen and she had also developed a calcification inside her right adrenal gland. Her ACTH level had remained elevated but as no clinical symptoms were observed, she was observed without medication.

Author comment: *"Addison's disease occurred* as a *complication of active extra-adrenal gland tuberculosis simultaneously, and furthermore the administration of [rifampicin] induced adrenal crisis in the clinical course."*

Yokoyama T, et al. Addison's disease induced by miliary tuberculosis and the administration of rifampicin. Internal Medicine 48: 1297-1300, No. 15.2009-Japan 801154901

[1] Epidemiology of tuberculosis. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Centers for Disease Control and Prevention National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Division of Tuberculosis Elimination Atlanta, Georgia 2008. Available at: http://www.cdc.gov/tb/education/ssmodules/pdfs/module2.pdf

[2] WHO media centre, Fact sheet N°104 Updated October 2013. Available at: http://www.who.int/mediacentre/factsheets/fs104/en/ viewed 25/2/2014

[3] Centre for disease control and prevention, treatment for latent TB infection. Available at: http://www.cdc.gov/tb/topic/treatment/ltbi.htm viewed 25/2/2014

[4] Nigeria Tuberculosis Fact Sheet. Available at http://photos.state.gov/libraries/nigeria/487468/pdfs/January%20Tuberculosis%20Fact%20Sheet.pdf viewed 25/2/2014

[5] Stop TB partnership, Global Drug-resistant TB initiative(GDI) http://www.stoptb.org/wg/mdrtb/ viewed 25/2/2014

[6] Stop TB partnership TBHIV working grouphttp://www.stoptb.org/wg/tb_hiv/

[7] WHO Drug-resistant tuberculosis.Frequently asked questions January 2012. Available at http://www.who.int/tb/challenges/mdr/tdrfaqs/en/ viewed 25/2/2014

[8] WHO MDR TB 2013 update. Available at:http://www.who.int/tb/challenges/mdr/MDR_TB_FactSheet.pdf viewed 25/2/2014

[9] CDC Multidrug-Resistant Tuberculosis (MDR TB) and Extensively-Drug Resistant (XDR) TB available at: http://www.cdc.gov/tb/publications/webcourseswebinars/mdrandxdrtb/transcript.htm viewed 25/2/2014

[10] CDC Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm viewed 25/2/2014

[11]FDA News Release Dec. 31, 2012. Available at:http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm333695.htm viewed 25/2/2014

[12] Kwan, C. K. et.al. HIV and Tuberculosis: a Deadly Human Syndemic. Clin Microbiol Rev. Apr 2011; 24(2): 351–376. doi: 10.1128/CMR.00042-10 PMCID: PMC3122491. available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3122491/

[13] C. Padmapriyadarsini et.al. Diagnosis & treatment of tuberculosis in HIV co-infected patients. Indian J Med Res. Dec 2011; 134(6): 850–865. doi: 10.4103/0971-5916.92630 PMCID: PMC3284094 available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3284094/

[14] Living with HIV, dying from tuberculosis. Available at http://www.stoptb.org/assets/documents/resources/publications/acsm/TB_HIV_Brochure_Singles.pdf viewed 25/2/2014