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The standard treatment for latent tuberculosis infection, nine months of daily isoniazid, is effective at preventing active tuberculosis; however, its full benefits are limited by non-adherence. A shorter intermittent regimen of rifapentine plus isoniazid once weekly for three months is equally effective as the standard regimen in animal models. This regimen facilitates the use of directly observed therapy, a method that significantly improves adherence. The Center for Disease Control is sponsoring Study 26 to test the effectiveness and tolerability the three-month rifapentine based regimen in latently infected persons with risk factors for progression to active tuberculosis. This thesis will describe the background rationale and methods for the clinical trial, and the internship experience.

A STUDY OF THE EFFECTIVENESS AND TOLERABILITY OF WEEKLY RIFAPENTINE/ISONIAZID FOR THREE MONTHS VERSUS DAILY ISONIAZID FOR NINE MONTHS FOR THE TREATMENT OF LATENT TUBERCULOSIS INFECTION

Jessie Lemp, B.S.

APPROVED:

Patricia A. Gwartz
Major Professor

Committee Member

Walter McConathy
Committee Member

University Member

Chair, Department of Biomedical Sciences

Dean, Graduate School of Biomedical Sciences

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Jessie Lemp, B.S.

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CHAPTER I

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is the second leading infectious cause of death in the world. Approximately 2 million people continue to die each year from this curable disease. It is also estimated that one third of the world's population, 1.7 billion people, are infected with the latent (clinically silent) form of *M. tuberculosis*.[1] Treatment of latent tuberculosis infection (LTBI) significantly reduces the risk that TB infection will progress to TB infectious disease, and therefore is essential to the control and elimination of TB.[2] Specific groups of infected individuals, including recently infected persons and immunosuppressed persons, are at a higher risk of progressing to active TB disease. It is important that high-risk TB infected patients immediately begin and complete an entire course of preventative therapy.

Since the TB outbreak of the early 1990's, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have taken an active role in global TB control and elimination. One of their initiatives is to globally expand short-course directly observed therapy (DOT), a treatment approach that has been highly successful at controlling TB in countries that have adopted it.[3] DOT is a strategy for ensuring patient adherence, and it requires a health care provider or worker to watch the patient

swallow each dose of their antituberculosis medication.[4] The current standard treatment regimen for LTBI is nine months of daily isoniazid (INH).[5] A series of randomized, placebo-controlled clinical trials have shown that this regimen reduces the risk of active TB by 60-90% in immunocompetent individuals; however, its average efficacy of 65% is limited by poor patient adherence to the long course of treatment.[6] Implementing directly observed therapy (DOT) to improve patient compliance to latent infection treatment is not feasible with the 9-month daily INH drug regimen, which calls for ingestion of a minimum of 240 doses.

The Center for Disease Control (CDC) is supporting research on short-course, intermittent drug regimens for the treatment of LTBI to which DOT can cost-effectively be applied. Rifapentine (RPT) is currently approved by the Food and Drug Administration (FDA) to treat active tuberculosis; however, it is now being evaluated in short-course, intermittent treatment regimens for latent TB infection. Results in animal models have shown three months of once weekly RPT/INH to be at least equivalent to standard treatment regimens for LTBI.[6-8] DOT is feasible with the short-course, intermittent RPT/INH regimen, and may improve both patient adherence and average effectiveness of this regimen compared to other regimens for LTBI.

The primary focus of this six-month internship was on Tuberculosis Trial Consortium (TBTC) Study 26. This actively enrolling, open-label phase III study is comparing the effectiveness (based on intent-to-treat) of a three-month regimen of weekly rifapentine and isoniazid (3RPT/INH) administered under DOT to the effectiveness of nine months of daily self-administered isoniazid (9INH) at preventing

active TB in high-risk latent infected patients. This study is also comparing the tolerability and completion rates, as well as efficacy based on completer-compliers of 3RPT/INH versus 9INH. The short course 3INH/RPT regimen administered under DOT will likely become the new standard treatment regimen for LTBI if it is at least as effective and tolerable as the current standard of 9INH.

Table 1

Table of Abbreviations

Term	**Abbreviation**
Tuberculosis	TB
Latent Tuberculosis Infection	LTBI
Multi-drug Resistant Tuberculosis	MDR-TB
Directly Observed Therapy	DOT
Self-administered Therapy	SAT
Isoniazid	INH
Rifampin	RIF
Rifapentine	RPT
Pyrazinamide	PZA
Ethambutol	EMB
Streptomycin	SM
Moxifloxacin	MOXI
Centers for Disease Control	CDC
Tuberculosis Trials Consortium	TBTC
American Thoracic Society	ATS
World Health Organization	WHO
Food and Drug Administration	FDA
3 months of weekly Rifapentine plus Isoniazid	3RPT/INH
9 months of daily Isoniazid	9INH
Tuberculin Skin Test	TST
Acid Fast Bacilli	AFB
Bacilli Calmette-Guérin vaccination	BCG vaccination
Interleukin -1, 12, 2	IL-1, IL-12, IL-2
Antigen Presenting Cell	APC
Interferon gamma	INF-γ
Major Histocompatibility Complex	MHC

Term	Abbreviation
Tumor Necrosis Factor alpha	TNF-α
Human Immunodeficiency Virus	HIV
Protease Inhibitor	PI
Non-nucleoside Reverse Transcriptase Inhibitor	NNRTI
Enzyme-Linked Immunosorbent Assay	ELISA
Real-Time Polymerase Chain Reaction	RT-PCR
Aspartate Aminotransferase	AST
Serum Glutamic-Oxaloacetic Transaminase	SGOT
Enzyme-Linked ImmunoSPOT	ELISPOT
Adverse Event	AE
Serious Adverse Event	SAE
Institutional Review Board	IRB
Tuberculosis Control Clinic	TCC
University of North Texas Health Science Center	UNTHSC
Case Report Form	CRF
Quality Assurance	QA

CHAPTER II

TUBERCULOSIS

Background

Transmission

Mycobacterium tuberculosis, or tubercle bacillus, is the thin, rod-shaped pathogen responsible for tuberculosis. An infectious TB patient transmits this communicable disease by expelling tiny airborne droplet nuclei into the air that another person breathes in. The infectious patient who transmits tuberculosis is known as the source/index case, while the persons exposed to the source case are termed contacts of a TB case.[5]

Several characteristics increase the probability of transmission and infection to the contact patient. From a quantitative approach, the probability of infection depends on the concentration of tiny droplet nuclei in the air in relation to the volume of air inhaled by contacts. The number of droplet nuclei in the air suitable for alveolar deposition is influenced by the cavitary, pulmonary form of the disease, and by respiratory maneuvers such as coughing, sneezing, singing, and speaking.[9] The persons at highest risk of becoming infected with TB are close contacts of a source case with smear positive tuberculosis, a disease stage discussed later. Foreign-born persons from places that have high TB rates (Asia, Africa, Latin America, and Eastern Europe) are also at a higher risk for exposure to TB. Additionally, infants, children and adolescents have an increased risk of becoming infected with TB when exposed.[5]

Certain environmental conditions and settings influence the risk of acquiring infection. Poor ventilation, crowding, and/or prevalence of people with risk factors for tuberculosis make correctional facilities, nursing homes, homeless shelters, health care facilities and immigration camps high-risk settings for TB exposure and infection. Ultraviolet irradiation and sufficient room ventilation, as well as proper infection control, may reduce tuberculosis transmission in these settings.[9]

Pathogenesis

Infection may begin when tiny droplet nuclei containing tubercle bacilli are breathed in and travel down the bronchial tree to settle in the pulmonary alveoli of the contact patient. Tubercle bacilli promote their own phagocytosis by non-immune, resident alveolar macrophages via activation of complement, C3-cleaving opsinization, or macrophage fibronectin receptors. If the alveolar macrophages are able to quickly kill all of the ingested bacilli, then no infection occurs.[9]

Most virulent strains of *M. tuberculosis*, however, have strain-specific attributes, which allow them to escape the intrinsic inhibitory mechanisms of non-activated phagocytic cells. The proliferation of bacilli within the nurturing environment of an alveolar macrophage eventually results in destruction of the host cell and escape of tubercle bacilli into the extracellular environment of the alveoli. During the struggle, the alveolar macrophages release cytokines IL-1 and IL-12, which attract and stimulate T lymphocytes. The macrophages also release chemokines, which attract additional macrophages, dendritic cells, and monocytes from the blood to engulf the released bacilli.[9] The tubercle bacilli logarithmically multiply within these immune-effector

cells, as they are transported from the primary infection site to the hilar lymph nodes, where the immune response largely progresses. Hematogenous dissemination of bacilli is also likely to occur during the primary infection, with the most common sites of seeding being the apices of the lung, the kidneys, the brain, and the bone.[10]

Aside, from the activation of complement during the initial step of phagocytosis, humoral immunity (antibody mediated) does not play a significant part in defending the host from *M. tuberculosis*. Instead the host protects itself through a cell-mediated immune response and delayed-type hypersensitivity initiated by antigen presenting cells (APCs). The APCs involved in the immune response are primarily the monocytes and dendritic cells. T-helper cells play the major role in tuberculoimmunity by recognizing and activating APCs that present tubercle antigen in association with major histocompatibility complex class II (MHC-II) molecules. T-helper cells activated by APCs release cytokines IL-2 and IFN-γ. IL-2 is both an autocrine stimulant and a stimulant of other T-cells.[9] IFN-γ activates the antigen presenting macrophage giving it greater tuberculostatic and tuberculocidal activity.[11] Cytotoxic T-cells are also activated, but to a lesser extent, by MHC class I associated APCs. Cytotoxic T-cells induce lyses of incompetent macrophages unable to control the proliferation of bacilli. The released tubercle bacilli can then be ingested by more adroit macrophages.[9]

Once in place, the delayed-type hypersensitivity immune response peaks 48-72 hours after peptide introduction and is the basis behind the TB skin test.[9] It may take 2 to 10 weeks from the time of initial infection for the host to orchestrate the entire cell-mediated immune response and develop a positive reaction to the tuberculin skin test.[5]

As the immune response evolves, activated macrophages release TNF-α, which stimulates the formation of a granuloma at the site of primary infection in the lung and at extrapulmonary lesion sites. The granuloma has a caseating (cheese-like) center of tuberculostatic, acidic milieu surrounded by concentric rings of increasingly competent macrophages and lymphocytes. In most immunocompetent hosts, the outermost macrophages are able to control the proliferation and dissemination of intracellular bacilli, and eventually the viable bacilli become dormant and the granuloma scars over.[9] This event marks the stage of latent tuberculosis infection. Once a person is infected with tubercle bacilli, they will always have a positive reaction to the TB skin test. Persons with LTBI, however, are not infectious, do not have symptoms of TB, and are not considered a case of TB.[5]

The major determinants of the type and extent of TB disease are the patient's age and immune status, the virulence of organism, and the mycobacterial load. Immunosuppressed individuals, infants, and elderly adults may be unable to elicit an immune response capable of halting the proliferating bacilli of the primary infection. They can become clinically ill with primary progressive pulmonary or extrapulmonary TB disease within weeks to months following the primary infection.[9]

Other individuals with LTBI may experience reactivation tuberculosis months to years later. Reactivation tuberculosis most commonly occurs in old lesions located in the apices of the lungs, but might also occur at extrapulmonary sites. Although 75% of all TB cases are exclusively pulmonary, 18% are extrapulmonary only, and 7% are both.[9] Reactivation disease initiates when viable bacilli still present in the old lesion begin to

overcome immune defenses and kill the phagocytes they are proliferating in. Proteolytic enzymes along with tumor necrosis factor-α (TNF-α) are released causing the center of the lesion to undergo caseous necrosis with liquidification. The bacilli begin to proliferate extracellularly causing inflammation and eventually rupturing the lesion. The necrotic residue and bacilli rush out of the lesion leaving a cavity behind. The bacilli may enter the airways where they are expelled from the host to form droplet nuclei. They also may traverse the lung to form new lesions that will eventually turn into cavities. If left untreated, the damage done to the lungs will result in respiratory inadequacy.[9]

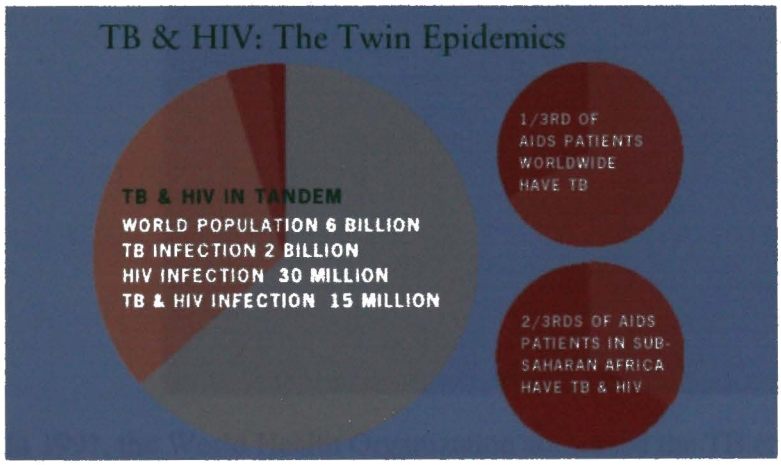
Certain risk factors increase the probability that reactivation disease will occur in patients with LTBI. Reactivation occurs in 5% of immunocompetent TB infected persons within the first two years after infection, and in 10% of these persons over a lifetime. Consequently, recent TB infection is a risk factor for progression to TB disease. Contact investigations are conducted when a case of TB is diagnosed in order to target and treat those who may have been recently exposed to the TB case.[5]

Another straightforward risk factor is the presence of apical scarring on a chest-radiograph left from the primary infection or from previous untreated TB. Pulmonary reactivation disease usually begins in the apical and posterior segments of the upper lobes or in the superior segments of the lower lobes. This distribution may be related to the higher oxygen tension or the reduced perfusion and lymphatic clearance in these segments.[9]

A third powerful risk factor for reactivation disease is co-infection with HIV. Persons infected with both LTBI and HIV have a 7%-10% risk each year for developing

TB disease.[5] There were 2 million deaths due to TB in 2000, and 13% of those who died were co-infected with HIV.[11] *Figure 1* from the Global Alliance for Tuberculosis Drug Development, shows the combined prevalence of HIV and TB.[12] Other risk factors include substance abuse, illicit drug use, cigarette smoking, diabetes mellitus, cancers of the head and neck, renal disease, silicosis, prolonged corticosteroid or other immunosuppressive therapy, malnutrition, and low body weight.[5] Persons who are in any of these risk groups should be targeted and tested for LTBI, and then subsequently treated.[13]

Figure 1

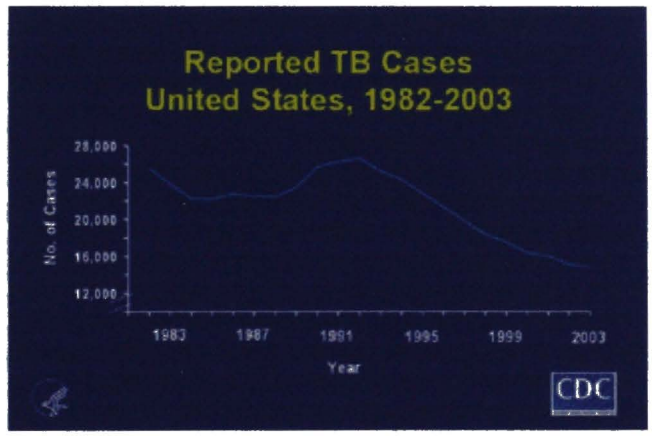


Epidemiology

Advances in anti-tuberculosis drugs in the 1950's led to a steady decline of the "white plague" in most parts of the world. As a result, the TB epidemic was neglected for several decades despite the impact it still had on developing nations. After decades of

steady decline resulting in a total reduction of 74% in the annual incidence of tuberculosis in the U.S. from 1953 to 1985, a rebirth of the disease transpired in the late 1980's. As shown in *Figure 2*, between 1985 and 1992, annual tuberculosis incidence in the U.S. increased 20.1%.[14] The reasons for the TB increase in the US and globally were the HIV epidemic, the growth of poverty, and immigration from developing countries. Seriously fatal outbreaks of multi-drug resistant TB were also reported during this time.[15] Economic globalization had increased the dynamic flow of people and pathogens, forcing the need to subsequently globalize TB control.

Figure 2



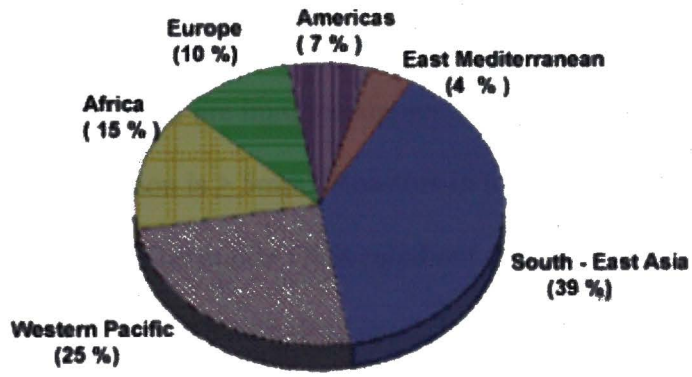
In 1991, the World Health Organization addressed the TB crisis, and set global targets for TB control for the year 2001 of detecting at least 70% of estimated infectious cases and curing at least 85% of these. The Global Partnership to Stop TB has committed to meeting these targets by the extended deadline of 2005. They propose to attain these targets through an accelerated plan of expanding DOT, adapting it to the challenges of HIV-related TB and multi-drug resistant TB, and developing new diagnostics, drugs and vaccines for TB.[3]

The U.S. has experienced success in getting TB back under control through government funding to improve TB control programs and to develop new drugs, diagnostics, and vaccines. During 2002, the TB case rate reported by the CDC from the U.S. was 5.2 cases per 100,000, representing a 5.7% decrease from 2001 and a 43.5% decrease from 1992 when the number of TB cases and the TB case rate last peaked in the United States. During 2003, the CDC reported only a slightly lower incidence rate from 2002 with 5.1 cases per 100,000 persons. This represents the smallest annual decrease since 1992, and is still far above the national goal of 3.5 cases per 100,000 persons. Some states, including California, New York, and Texas, even reported increases in cases from 2002 to 2003. Foreign-born persons accounted for 53.3% of the national case total, with the five most common birth countries being Mexico, Philippines, Vietnam, India, and China. Among U.S. born persons, the highest rate of TB reported in 2003 were among racial/ethnic minorities, with the black population representing 45% of the cases.[16] These trends demonstrate the persistent need for TB control. Now that TB case incidence is steadily on the decline in the U.S., treating LTBI is one of the main concerns for eliminating TB in the U.S.

Although TB case numbers have steadily declined in North and South America, western and central Europe, and the Middle East in the past decade, some regions have reported increases in cases. Figure 3 depicts the percentage of Global TB cases by region in 1999.[17] While heavily populated South-East Asia has the greatest percentage of reported cases, Sub-Saharan Africa has the highest incidence rate of any region at 290 cases per 100,000 persons. This outrageous incidence rate is primarily due to the HIV

epidemic that is also plaguing the region.[11] Rates of HIV infection among TB patients exceed 60% in Botswana, South Africa, Zambia, and Zimbabwe.[11] The former Soviet Union has also experienced a surge in TB cases over the past decade due to socioeconomic changes and poor health care. Owing to the broken down health care system, ten percent of the total cases reported were multi-drug resistant, which is even more difficult to treat. The last global census of TB conducted in 2000, reported 8-9 million new cases, with 3-4 million of them being smear positive (extremely infectious cases). The global tuberculosis burden remains a major concern, even for the United States.

Figure 3 **Percentage of Global TB Cases by Region, 1999**



Source: WHO Geneva, Global Tuberculosis Control, WHO Report 1999

Diagnosis

Tuberculin Skin Test

Targeted testing for TB identifies persons with LTBI or TB disease who would benefit from treatment. Persons at a higher risk for TB exposure, infection, and progression to TB disease should be routinely tested for tuberculosis. The primary screening test for TB is the Mantoux tuberculin skin test (TST). Administration involves intradermal injection of 0.1 mL of liquid containing 5 tuberculin units of purified protein derivative into the forearm. The reaction to the tuberculin antigen is a delayed-type hypersensitivity response that results in an induration (hardened swelling) at the site of injection. The induration manifests from a collagen infiltrate of tuberculin-specific T-cells and monocytes. Interpretation of the TST is based on measurement of the induration (not erythema) 48-72 hours after administration.[18]

Patients who are HIV-positive, are recent contacts of a TB case, have lung fibrosis consistent with old TB, or are immunosuppressed are considered to have a positive skin test if the induration is $\geq$ 5mm. Reactors in this category should be prescribed treatment of LTBI after active TB is ruled out. Persons with an induration $\geq$ 10mm who are foreign born, are injection drug users, are residents or employees of high risk settings, have high-risk clinical conditions, or are children < 4 years old are also classified as having a positive skin test and should be considered for preventative therapy. In persons with no risk factors for TB, an induration $\geq$ 15 mm is a classified positive reaction. Prescribing treatment for LTBI to these patients is not a priority but it may be considered by discretion of the physician. A skin test conversion is defined as an

increase of ≥ 10mm of induration within a two-year period. Converters fall under the high-risk category, and should be prescribed preventative therapy.[5]

Certain factors lower the specificity of the tuberculin skin test. Infection with non-tuberculosis mycobacteria and vaccination with Bacille Calmette-Guérin (BCG) may give a false-positive reaction to the skin test. The BCG vaccination is a live attenuated mycobacterial strain derived from *M. bovis,* a member of the M. tuberculosis complex. The BCG vaccine is given to infants and children in high prevalence countries because it offers significant protection against severe forms of miliary and meningeal tuberculosis.[19] The BCG vaccine is not recommended in the U.S. because of the lower prevalence of TB, the insignificant effectiveness of the vaccine against pulmonary TB, and the loss of utility of the tuberculin skin test.[5] Tuberculin skin testing is not contraindicated for persons vaccinated with BCG, and such persons are candidates for preventative therapy if they are in a high risk category and produce an induration ≥ 10 mm.[5] The development of a more effective vaccine to replace BCG would be a major contribution to global elimination efforts.

False-negative reactions to the tuberculin skin test may occur in immunosuppressed persons, very young children, and very recently infected persons. The anergic state (decreased immune responsiveness) of immunocompromised patients (e.g., HIV positive patients) may cause a false-negative skin test. TB infection and disease should not be ruled out in these high-risk, non-reactive individuals, and treatment should still be considered. False-negative reactions are also commonly encountered in recent contacts of a TB case. Recently exposed persons who do not react to the initial

tuberculin skin test should be retested approximately 10 weeks after exposure, to allow enough time for the immune response to develop.[5]

The limitations of the TB skin test, which include its low sensitivity, decreased specificity, delayed results, and subjective nature, suggest the need for new tests to diagnose TB and LTBI. QuantiFERON© test and ELISPOT are two promising *in vitro*, serological tests that can diagnose LTBI based on measuring the amount of INF-γ released or identifying the number of lymphocytes that produce INF-γ respectively in response to tuberculosis antigens. A current study, which the internship site is actively involved in, is comparing these three tests for their accuracy at detecting LTBI and active TB. It is hypothesized that QuantiFERON© and ELISPOT, which both require only one patient visit, may be more specific and less susceptible to interpretation bias than TST.[20] Results from this study should be available next year.

Clinical Signs and Symptoms

Patients with a positive skin test as well as patients with suspected TB should be further evaluated to confirm or rule out TB disease. It is important that TB disease is ruled out in high-risk tuberculin skin reactors before preventative therapy is initiated. Patients are first assessed for the respiratory symptoms of active pulmonary TB, which include prolonged and productive cough, chest pain, hemoptysis (blood in phlegm), shortness of breath, and hoarseness (laryngeal TB).[9] TB should also be considered in patients with systemic symptoms including fever, chills, night sweats, appetite loss, weight loss, and fatigue.[5] While young infants and adolescents are more likely to

experience the classic symptoms of pulmonary disease, school-age children often have clinically silent disease, although their chest x-rays will prove otherwise.[21]

Chest Radiograph

The next step in diagnosis is to take a posterior-anterior chest x-ray of positive skin test reactors and TB suspects. The chest x-ray of a patient with LTBI is either completely normal, or it may show evidence of the primary infection in the form of a small, calcified nodule called a Ghon-focus. Neither of these visual remnants puts the patient at greater risk of reactivation TB than does the TB skin test alone. On the other hand, the presence of apical scarring on the chest radiograph, resulting from hematogenous seeding during the primary infection, does increase risk of subsequent pulmonary tuberculosis.[10] A recent article published in the New England Journal of Medicine by C.R. Horsburgh, Jr., M.D., reports that the lifetime risk of reactivation tuberculosis is 20 percent or more among persons with an induration of 10mm or more on a tuberculin skin test and evidence of apical fibrosis on the chest radiograph.[13] Such persons should be prescribed preventative therapy once further diagnostics rule out active TB.

The most common manifestation of post-primary (reactivation) pulmonary TB on a chest x-ray is heterogeneous fibronodular shadowing (infiltrates) positioned in the apical and posterior segments of the upper lobes and the superior segments of the lower lobes of the lungs. The infiltrates are often accompanied by one or more cavities, which are hollowed out spaces in the lung that result from granuloma necrosis and

liquidification. The presence of cavities is indicative of increased infectiousness of the patient.[9]

Children and HIV positive or severely immunosuppressed individuals with pulmonary TB may have atypical radiographic findings. The primary feature of the pediatric TB radiograph is lymphadenopathy, which is not as common in adult cases. The enlarged nodes may partially obstruct the bronchioles causing atelectasis of the affected lobar segment that can be visualized on the chest x-ray. Infiltrates are present in two-thirds of pediatric TB cases; however, they appear as homogenous consolidations in segmental or lobular distribution.[21]

Ten to twenty percent of severely immunosuppressed HIV/AIDS patients co-infected with pulmonary TB have completely normal radiographs, adding to the difficulty of diagnosing TB in this group. The other 80-90 percent have radiographic abnormalities that often differ from the classic abnormalities. The chest x-ray of a co-infected patient may demonstrate lower zone infiltrates, miliary shadowing (innumerable spread of non-calcified nodules), pleural effusions, and lymphadenopathy.[10]

Radiographic abnormalities may suggest active TB; however, they cannot diagnose TB. Other pulmonary diseases or TB disease states may produce radiographic abnormalities similar to those common to active pulmonary TB. However, a normal chest radiograph is useful at ruling out pulmonary TB in a person with a positive skin test and no symptoms of TB.[19] The chest x-ray can also be used to monitor treatment response in persons with active TB, as it should improve over the course of treatment.

Microscopy

When the chest x-ray is abnormal, a series of sputum specimens is collected on three consecutive days for smear examination and culture. Sputum is usually brought up by a deep cough. Patients unable to spontaneously produce sputum may be induced to cough by inhaling a heated saline aerosol. For children and other persons unable to produce induced sputum, morning gastric aspirations can be used to collect specimens of swallowed sputum.[5]

All mycobacteria species have a unique "acid-fastness" staining quality due to the high lipid content in their cell walls. *M. tuberculosis* and three other closely related mycobacteria species *(M. bovis, M. africanum,* and *M. microti*) can all cause TB disease and make up the *M. tuberculosis* complex.[5] After a sputum specimen is collected, these species may be isolated by a centrifuge and then smeared on a glass slide. The smear is then stained with a lipid staining dye such as Ziehl-Neelsen, and subsequently treated with an acid alcohol. Mycobacteria resist decolorization by the acid alcohol, and these acid-fast bacilli (AFB), if present, appear as red rods under the microscope.[9] There are two disadvantages of the microscopy diagnostic technique. For one, it is nonspecific due to the fact that sputum containing non-tuberculosis mycobacteria (e.g. *M. avium complex*) will also be positive for AFB. Secondly, it is less sensitive than culture in detecting mycobacteria in the collected sputum.[9] Patients with less extensive, noncavitary disease have a substantial possibility of producing sputum negative for AFB, even though viable bacilli are present. Once *M. tuberculosis* is determined by culture to be the disease culprit, smear status does have the advantage of indicating infectiousness of the diseased

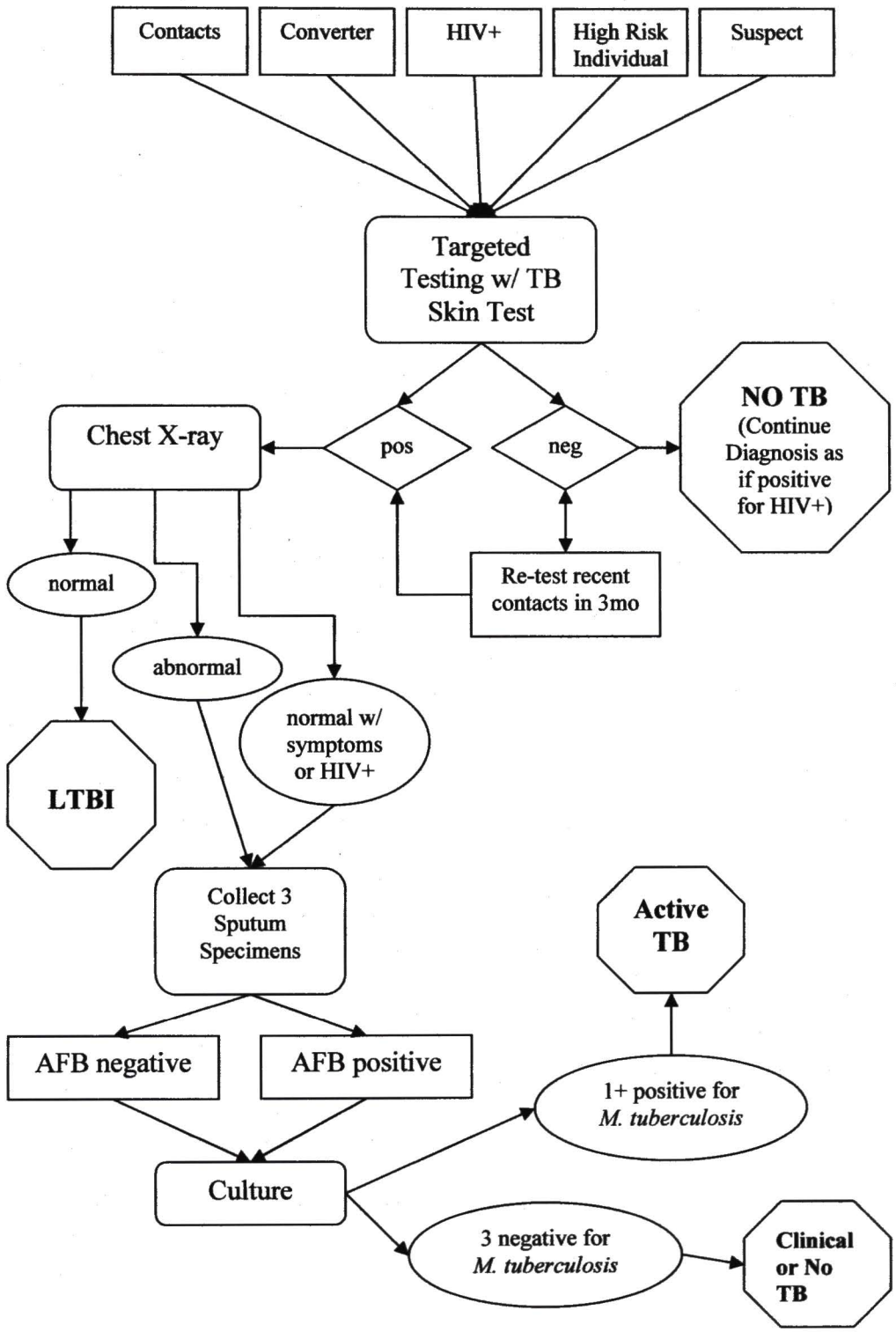
patient. Smear-positive cases are more infectious and more fatal than smear-negative cases.[11]

Cultivation and Susceptibility Testing

The "gold standard" in diagnosing active TB is specimen culture. Cultivation is useful not only for species identification, but also for drug-susceptibility testing and monitoring response to therapy. Unfortunately, *M. tuberculosis* has an extremely slow growth rate and optimal use of standard culture techniques allows for accurate species and susceptibility determination in 18-21 days. New liquid medium systems such as the BACTEC Radiometric System can create growth in 4 to 14 days, and produce more rapid species identification. The cultured species is identified using nucleic acid probes specific for *M. tuberculosis* complex, *M. avium* complex, and others. Species within the *M. tuberculosis* complex cannot be differentiated by this technique. Specimen collections are simultaneously tested for growth on mediums containing different antituberculosis drugs (typically isoniazid and rifampin) to determine susceptibility status. New techniques are being studied for their ability to produce accurate results in a shorter period of time.[9] Three consecutive negative cultures usually indicates absence of active TB, therefore, culture results can be used to rule out active TB or to monitor response to treatment.[5] *Figure 4* on the following page depicts the process of diagnosing TB.[5]

Figure 4

Diagnosing Tuberculosis



Extrapulmonary TB

Diagnosing extrapulmonary TB is slightly different from diagnosing pulmonary TB. Patients with extrapulmonary TB will experience site-specific symptoms, and may or may not experience systemic symptoms. Specimens from the affected tissue (e.g. urine, cerebral spinal fluid, pleural fluid) are collected for culture and susceptibility testing. Patients with culture positive extrapulmonary TB, and without concurrent pulmonary or laryngeal TB, are generally non-infectious.[5] The most frequent cases of extrapulmonary TB are lymphatic, genitourinary, meningeal, bone-joint, and miliary (disseminated disease affecting two or more organs).[9] Extrapulmonary TB most commonly occurs among HIV infected patients as reactivation TB and among children soon after the primary infection. Approximately 25-35 percent of children affected by TB have an extrapulmonary form, with meningeal and miliary TB (affecting the lungs, spleen, and bone marrow) being the most common.[21]

Treatment for Active Tuberculosis

The preferred treatment for active, pan - susceptible TB (TB susceptible to all first-line TB drugs) is a six-month regimen consisting of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and either ethambutol (EMB) or streptomycin (SM) for two months, followed by isoniazid and rifampin for four months. This regimen produces cure rates of 95% or more if properly adhered to.[22]

The multi-drug, 2-month intensive phase is crucial for accelerating the response to treatment and preventing the advent of drug resistance. Positive cultures usually convert

to negative by the end of the intensive phase for patients with drug susceptible TB who adhere to treatment. Each of the drugs included in the intensive phase plays an important role in combating tubercle bacilli, however, INH and RIF are the most significant. INH provides the highest early bactericidal effect and is largely responsible for the rapid reduction of infectiousness that occurs within the first couple of months of treatment.[23] RIF demonstrates the greatest bacteristatic activity of all the drugs, and therefore has the greatest impact on reducing the duration of therapy required to prevent relapse.[9] Pyrazinamide (PZA) is also a major sterilizer and is essential for reducing the duration of treatment from 9 to 6 months.[9] Ethambutol (EMB) and streptomycin (SM) both have significant bactericidal effects and are added to the intensive phase to prevent the emergence of drug resistance when there is a possibility that the invading strain is INH-resistant.[5] Because the intensive phase requires so many drugs at relatively high doses, the pill burden is large.

Adherence and DOT

Nonadherence to prescribed treatment regimens for TB is a major problem in TB control, as it may be the cause of relapse, prolonged transmission periods, and development of drug resistance. Treatment failure due to nonadherence can cause higher patient treatment costs and amplified tuberculosis transmission costs.[4] Patient adherence may be improved by patient education, case management, use of incentives (food coupons, transportation passes, or housing), providing fixed-dose combination capsules, and implementing directly observed therapy (DOT).[5]

DOT requires health care employees or outreach workers to deliver and observe patients taking all their treatment doses. Based on various studies, DOT has been shown to reduce the development of drug resistance and prevalence of multi-drug resistant TB, reduce the cost per case of TB treated, improve the rate of treatment completion, and reduce the occurrence of relapse after completing treatment.[24] The CDC supported a retrospective study of two concurrent patient cohorts in the U.S., one receiving 6-month treatment by DOT and another by self-administered therapy (SAT). The results of the study on the proportion of patients who completed treatment at 8 and 12 months showed relative superiority of DOT over SAT. Completion rates at 8 and 12 months were 52% and 70% respectively for DOT versus 35% and 53% for SAT.[24]

Opponents are concerned that DOT is intrusive and unaffordable. On the other hand, quality DOT programs combined with incentives can be looked upon as an enhancement to health service rather than an infringement on individual liberty.[22] DOT is facilitated by short course, intermittent drug regimens. Short-course DOT reduces both the total number of doses and the number of healthcare worker encounters. The majority of the treatment regimens for drug-susceptible TB can be administered intermittently if DOT is applied.[5] For example if DOT is used with the 6-month TB treatment regimen, four drug therapy may be administered daily for two weeks and then twice-weekly for six weeks, followed by twice-weekly therapy with INH and RIF only for the final four months.[5] The DOTS strategy has been ranked by the World Bank as one of the "most cost-effective of all health interventions," as it reduces the costs associated with nonadherence. According to a cost analysis by Weis S.E., DOT should be applied

universally (to all patients), and not selectively in order to maximize its benefits and cost-effectiveness.[4]

Under the influence of the WHO, 155 countries were implementing the DOTS strategy in 2001, up from only 10 in 1990, and treatment success under DOTS was at 82% in 2000.[3] The impact of DOT programs in the U.S. can be seen in partial by the reduction of the number of TB cases in the 1990s by about 7.8% per year in concert with an increase in the proportion of patients receiving DOT from 4% in 1990 to over 70% by 2000.[22]

Drug Resistance

There are two types of drug resistance in relation to M. tuberculosis, primary and acquired. Primary resistance can be observed in patients with active TB who have never received any prior treatment for TB. It is inferred that these patients were infected with a drug resistant strain of M. tuberculosis. Acquired drug-resistance may develop in patients who harbor tubercle bacilli that shift from a susceptible phenotype to a resistant phenotype during or after a course of inadequate treatment.[9] Drug-resistant TB is caused by inconsistent or partial treatment as a result of non-adherence, improperly prescribed treatment, or unreliable drug supply.[22]

Acquired drug resistance begins with spontaneous mutations at specific loci that give rise to tubercle bacilli phenotypes resistant to different drugs. This phenomenon, though rare, is neither dependent on nor accelerated by the presence of drugs. If actively dividing bacilli are treated with only one drug, for instance monotherapy with INH, mutant bacilli resistant to INH are given the opportunity to replicate and become the

dominant strain while the susceptible organisms are killed off. Thus, the importance of properly diagnosing LTBI before prescribing preventative monotherapy with INH becomes clear, to avoid emerging drug resistance in patients who may have active TB. Of equal importance is to never to add one drug at a time to a failing treatment regimen, as this may have the same effect as monotherapy.[5]

When two or more susceptible drugs are given in chorus, each helps prevent the emergence of strains resistant to the other. One of the rationales behind using multiple drugs in treating active TB, especially in the intensive phase, is to avoid the emergence of drug resistance.[22] However, even when multiple drugs are prescribed, taking them at sub-inhibitory concentrations gives resistant mutants a selective growth advantage. This circumstance is not uncommon when treatment involving several pills at each dose is self-administered. Stopping and restarting multiple drugs also facilitates the growth of resistant mutants due to the differing post-antibiotic lag phases of the drugs. The post-antibiotic lag phase is the length of time it takes bacilli to restart growth when drugs are stopped, and it differs for each drug. Thus mutants resistant to drugs with longer lag phases have a selective growth advantage after a drug regimen is stopped.[23]

INH-resistant strains and RIF-resistant strains cause the most concern due to the fact that INH and RIF are the most potent drugs for treating TB. If patients with one of these drug resistances are not treated by DOT with at least three susceptible drugs, multi-drug resistance is likely to develop. Multi-drug resistant TB (MDR-TB) is defined as resistance to both INH and RIF, and it is very problematic to treat. In order to treat

MDR-TB, second line drugs that are more expensive, more toxic, and less effective than first-line drugs must be used in regimens that are up to 24 months long.[5, 10]

Special Circumstances

Certain forms of extrapulmonary TB, including bone and joint TB, miliary TB, and TB meningitis should be treated for a minimum of 12 months.[5] For HIV-positive patients receiving protease inhibitors or non-nucleoside reverse transcriptase inhibitors, rifabutin may be substituted for rifampin in the intensive four-drug regimen, due to rifampin's potent interactions with anti-retroviral drugs. If necessary, a non-rifamycin regimen including both EMB and SM may be prescribed in order to comply with anti-retroviral therapy. Finally, PZA and SM are contraindicated in pregnant women due to their unknown (PZA) or harmful (SM) effects on the unborn fetus. Pregnant women should take a 9-month regimen of INH, RIF, and EMB.[5]

The CDC is sponsoring clinical trials to test new antituberculosis drugs and regimens that have the potential to shorten the length of therapy, and treat drug resistant tuberculosis. One candidate is moxifloxacin (MOXI), a fluoroquinolone with bactericidal activity similar to rifampin. MOXI is currently being studied in active TB patients for its ability to improve culture conversion rates. MOXI is an inhibitor of DNA gyrase and is highly active even against strains of *M. tuberculosis* resistant to other first-line drugs.[25]

Adverse Drug Events

Toxic reactions to one or all of the drugs used to treat TB may occur. INH is most commonly associated with causing peripheral neuropathy and hepatotoxicity, the former of which can usually be prevented by concurrently taking pyridoxine (vitamin B6

supplements).[23] RIF interacts with several drugs, including methadone, contraceptives, and protease inhibitors and non-nucleoside reverse transcriptase inhibitors because it is an inducer of cytochrome P-450. RIF may also cause flu-like symptoms [23]. PZA can cause gout-like arthralgia. Ototoxicity and nephrotoxicity are adverse events associated with SM; therefore, audiometry should be routinely performed on patients taking SM. EMBs most serious side effect is optic neuritis. Visual acuity and color vision tests should routinely be performed when EMB is prescribed. If a patient develops toxicities to any of these drugs, the culprit drug should be identified and discontinued, and an alternative regimen prescribed.[5]

Treatment for Latent Tuberculosis Infection

The ATS and CDC currently recommend 9 months of daily isoniazid (INH) as optimal treatment for LTBI. Latent TB infection is usually diagnosed by a positive TST and a normal chest x-ray. Correctly diagnosing LTBI is necessary to avoid causing drug-resistant TB. Daily INH for twelve months has been shown to reduce the risk of progression to TB disease by as much as 90% in patients who complete a full course of therapy.[26] Due to low patient adherence because of the length of the treatment, an average effectiveness of 70% is suggested for a 9 to 12 month course of INH.[7] The protection offered by 9 months of INH is greater than for 6 months; however, the latter is sometimes preferred because it may be more cost-effective and results in greater patient adherence. Peripheral neuropathy and hepatitis, though uncommon, are associated with

the use of INH. In addition, the INH regimen is not suitable to treat persons exposed to INH-resistant *M. tuberculosis*, which is a common resistant strain.[7]

The INH regimen, though efficacious and inexpensive, is limited by poor patient compliance. It is sometimes difficult to convince patients to take daily medicine for nine to twelve months when they are not experiencing any symptoms. An investigation in Chicksaw County, Mississippi emphasizes the importance of completing the full course of preventative therapy. Between 1999 and 2002, Chicksaw County experienced higher and increased TB incidence rates as compared to the rest of the state, which reported decreased TB rates over the three years. Among the 16 reported cases in this small county between 1999 and 2002, five had been previously diagnosed with LTBI and offered treatment. All five had refused or stopped treatment, progressed to active TB and went on to become sources of infection for 10 more TB patients and 67 LTBI patients.[27] It is important that infected persons identified in a contact investigation complete a full-course of treatment for LTBI, because reactivation risk is greatest during the first two years after the initial infection. Chicksaw County would have greatly benefited initially from DOT for LTBI. DOT was actually implemented to treat the recently infected contacts identified after the investigation.[27] The Chicksaw County outbreak epitomizes the cost-effective benefits of DOT not only in treating active TB, but also in treating LTBI in high-risk populations when short-course, intermittent regimes are utilized.

To facilitate the use of DOT, shorter regimens involving the use of rifamycins have recently been approved for treatment of LTBI based on trials in HIV-positive persons co-infected with TB. Differences in antibacterial activities make rifamycins

more bactericidal than INH under certain conditions. Through inhibition of mycobacterial cell wall growth, INH exhibits early bactericidal activity against rapidly dividing bacilli. Rifamycins on the other hand are much more bactericidal than INH during spurts of metabolism, by binding to RNA polymerase and killing within seconds.[28] Two to three month regimens of rifampin plus pyrazinamide, administered daily or twice weekly, to HIV-positive, TB infected adults proved to be as effective as longer course INH treatment regimens for LTBI and produced superior adherence.[29] Based on this evidence, the RIF/PZA regimens were approved by the Food and Drug Administration (FDA) to treat LTBI. As of August 2003, the ATS and CDC no longer recommend the use of short course RIF/PZA in TB infected persons. Their decision was based on high rates of severe liver injury reported in patients treated for LTBI for two months with daily or twice-weekly RIF/PZA.[30]

Another derivative of rifampin, rifapentine (RPT), has been studied in animal models for the treatment of LTBI, and in humans during the continuation phase of treatment for TB disease. Rifapentine, like rifampin, is an RNA synthesis inhibitor with a similar minimal inhibitory concentration; however, it has a higher maximum plasma concentration and a much longer half-life than RIF. In one animal study comparing different rifamycin derivatives, the serum concentration of RPT at 144 hours after drug administration was still higher than the minimal inhibitory concentration of RPT against infected mice, which provides the possibility of widely spaced intermittent administration of RPT.[7] Based on colony forming unit (cfu) counts, RPT is more bactericidal against *M. tuberculosis* than RIF on a weight-to-weight basis. Another study by Chapuis et al,

confirmed that intermittent administration of 10 mg/kg of RPT up to only once fortnightly was active in mice. The same study showed that the addition of intermittently administered INH to RPT significantly enhanced the effectiveness of RPT in both normal (immunocompetent) and nude (immunosuppressed) infected mice.[8] The regimens tested in this study were daily INH for 26wks, daily PZA/RIF for 13wks, and RPT either alone or with INH, once weekly, fortnightly, or monthly for 13 or 26 weeks. Of all the regimens compared, once weekly RPT plus INH was the only regimen that rendered cultures negative in nude (immunosuppressed) mice after 13-26 weeks of treatment.[8] In the Cornell mouse model of latent tuberculosis, a model which demonstrates a closer approximation of LTBI in humans, preventive therapy of once-weekly INH plus RPT for 18 weeks was as effective as daily isoniazid therapy for 18 weeks, and more effective than monotherapy with weekly RPT for 18 weeks.[6] Because of the similarities in pharmacokinetics of rifamycins in mice and humans, antimicrobial activities of RPT observed in mice may be extrapolated more or less straight forwardly to humans.[7]

Once-weekly RPT plus INH in the continuation phase of TB treatment has been tested on humans in several clinical trials. A clinical trial in Hong Kong enrolled 592 Chinese patients with active TB who had completed the intensive phase of treatment. Patients were then randomized to receive six months of continuation therapy with one of the following regimens: thrice-weekly RIF/INH, once weekly INH/RPT, or INH/RPT given once every two of three weeks. Although RPT was well tolerated, it was associated with a higher rate of adverse events and treatment failure/relapse rates, which were 4% in the thrice-weekly RIF/INH regimen vs. 11% in the once-weekly INH/RPT

regimen. Unfortunately, during the study it was found that the Chinese manufactured RPT had sub-optimal bioavailability. Consequently, RPT doses were changed from 600 mg doses to 750 mg doses administered with food. It is still difficult, however, to interpret the results of the study.[31]

Results from a similar trial, USPHS Study 22, sponsored by the CDC Tuberculosis Trials Consortium (TBTC) have recently been published. Study 22 enrolled 1004 HIV-negative and 71 HIV-positive patients with drug-susceptible pulmonary TB. All patients received INH, RIF, PZA, and either EMB or SM during the first two months of treatment (intensive phase), and were then randomized during the continuation phase to receive either once-weekly RPT/INH or twice-weekly RIF/INH. HIV-positive patients were removed from the study after several subjects on the RPT/INH arm relapsed with rifampicin mono-resistant TB. Unadjusted analysis of results from the study showed that weekly RPT/INH was less effective at prevention of failure/relapse than twice weekly RIF/INH (9.2% vs. 5.6% relapse rate). Two risk factors for relapse, cavitation and positive sputum culture after the intensive phase, were unequally distributed between the groups. After a proportional hazard regression analysis was performed to control for these risk factors, the difference in treatment failure rates between the two groups was no longer significant. It was concluded that use of RPT/INH once a week in the continuation phase of TB treatment is effective in patients without major risk factors for relapse, and is a more cost-effective regimen for DOT.[32]

Investigators have suggested two possible reasons why once-weekly therapy with RPT 600mg/INH 900mg was not as effective as standard twice-weekly therapy in these

trials, which raises the question of what modification(s) could make this regimen more effective. One theory suggests that once-weekly INH may decrease the efficacy of the RPT/INH regimen, and may be the cause of the rifampicin resistance among HIV-positive participants of Study 22.[32] One solution to this problem could be to supplement RPT with a potent drug that has a longer half - life than INH, such as MOXI. Another solution is to supplement weekly RPT with daily INH; though this modification would not make DOT as feasible.[33] An alternative theory involves raising the dose of RPT. A dose of 600mg of weekly RPT was chosen for these trials based on animal studies and pharmacokinetic data; however, it appears to be less potent than twice-weekly-administered rifamycins. The higher protein binding of RPT compared to other rifamycins may not have been considered when calculating doses.[32] A prospective, randomized, double-blinded study was conducted to assess the tolerability of larger doses of 900mg and 1200mg of RPT using the same eligibility criteria and methods as Study 22. The study concluded that RPT 900mg once-weekly dosing is safe and well tolerated.[34] Consequently, this dose and dosing schedule was chosen for TBTC Study 26 to compare the effectiveness and tolerability of weekly RPT/INH for three months to daily INH for nine months for the treatment of LTBI.

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Study Drugs

Isoniazid

Isoniazid has the most potent early bactericidal activity of all antituberculosis drugs and is only active against mycobacteria. INH is a pro-drug that affects cell wall

integrity by inhibiting the synthesis of mycolic acids. Its bactericidal activity is accomplished through activation of a KatG gene that encodes the inhibiting catalase-peroxidase. Mutation in the KatG gene is the mechanism of resistance in 60-70% of INH resistant strains. INH travels into all tissue cells and bodily fluids, including granulomas. INH is metabolized in the liver by acetylation, and its metabolites are excreted in the urine within 24 hours. Genetically slow acetylators have longer serum half-lives and greater overall bioavailability of INH compared to rapid acetylators. Peak plasma concentration of INH is reduced following heavy meals. The recommended dosage of INH is 5 mg/kg body weight (maximum 300 mg) in daily treatment on up to 15 mg/kg (maximum 900 mg) in once-weekly treatment.[23]

INH is an antagonist of pyridoxine (Vitamin B6), and can interfere with its biological functions to cause peripheral neuropathy. The first complaints of this drug toxicity are numbness or tingling of the feet. Peripheral neuropathy is prevented by administration of a low dose of pyridoxine (50 mg) with each dose of INH.[23, 35]

Slow acetylators are predisposed to INH hypersensitivity (allergic) reactions, which include hepatitis, drug fever, asthma, and dermatitis. Elevated liver enzymes are frequent occurrences; however, clinical hepatitis occurs in less than 5% of patients. Risk of hepatitis substantially increases with acetaminophen and in patients > 35 years old.[23] Patients in this age category should receive routine blood draws for liver function tests in order to monitor for hepatotoxicity.[35] Adverse cutaneous reactions usually emerge as minor skin rashes or acneiform eruptions; however, they may progress to more serious skin problems such as exfoliative dermatitis.[36]

The total incidence of adverse reactions to INH has been estimated to be 5.4% with the most prominent reactions being cutaneous eruptions (2%), drug fever (1.2%), jaundice (0.5%), and peripheral neuritis (0.6%).[37] Other rare idiosyncratic reactions from INH (<1 per 1,000) include lupus erythematosus, rheumatic-like syndromes, and various hematologic disorders.[23] INH is safe for use in pregnant and breast feeding women.[5]

INH causes potentiation of some companion drugs through inhibition of their metabolic pathways. Some of the drugs whose effects are amplified by INH include anti-coagulants, anti-epileptics, tricyclic anti-depressants, and acetaminophen. INH can also cause hypersensitivity reactions upon interaction with certain fish and cheeses rich in monoamines.[23]

Rifapentine

Rifapentine (Priftin®) is a semisynthetic rifamycin derivative with antimicrobial activity similar to that of rifampin. The FDA approved RPT in 1998 to treat tuberculosis in immunocompetent patients. Both RPT and RIF are RNA synthesis inhibitors with potent bactericidal and sterilizing effects. RPT has an elimination half-life (14 hrs) almost four times longer than the half-life of rifampin.[38, 39] RPTs elongated duration of activity allows for less frequent dosing, however, it is cross-resistant with rifampin. Resistance to both RIF and RPT most commonly evolves from mutations in the RNA polymerase ß subunit, encoded by the rpoB gene.[23]

Unlike INH and RIF, the bioavailability of RPT increases 55% with food intake. RPT is hydrolyzed by an esterase enzyme found in the liver and blood to form the active metabolite 25-desacetylrifapentine. RPT and its major active metabolite are highly bound to plasma proteins, 97% and 93% respectively.[38] RPT is mainly eliminated by biliary excretion. The approved dosage of RPT is 600 mg administered twice-weekly during the intensive phase or thrice-weekly during the continuation phase of active TB treatment.[39] A larger dose of RPT, 900 mg once weekly, is currently being investigated in preventative treatment regimens. Rifapentine is more expensive than rifampin; however, long-term studies of cost-effectiveness of RPT are necessary.[39]

Side effects and adverse events associated with RPT are similar to those caused by RIF. The most common side effects of RPT are orange discoloration of urine and tears, and elevated liver enzymes. RPT induces INH hydrolase, which increases the formation of hydrazine causing increased risk of hepatotoxicity in patients receiving combination therapy with INH and RPT.[23] An immune-mediated flu-like syndrome has been reported in study patients taking high doses of RPT either alone or in combination. Symptoms of fever, nausea, shivering, faintness, headache, myalgia, and arthralgia, hypotension, and eye pain typically start one-two hours after a dose. The influenza-like syndrome appears to be more common in women than men, and occurrence increases with age. A sub-study of Study 26 is performing a clinical and immunologic assessment of possible hypersensitivity to INH and/or RPT.

RPT and other rifamycins induce cytochrome P-450 leading to faster elimination of the companion drug. Opposite to the interaction effects of INH, RPT decreases the

effects of several drugs it interacts with. The list of drugs whose effects are opposed by RPT is extremely long. Dose adjustments of the following drugs or of other drugs metabolized by the P-450 system may be necessary: anticonvulsants, antiarrhythmics, antibiotics, oral anticoagulants, antifungals, barbiturates, Beta-blockers, corticosteroids, hormonal contraceptives, PIs and NNRTIs, hypoglycemic agents, immunosuppressants, methadone, tri-cyclic antidepressants.[23] Patients are advised to practice barrier methods of birth control while taking RPT. While RIF is indicated for pregnant and breast feeding women, the effects of RPT on the unborn fetus have not yet been concluded.[38, 39]

Problem/Hypothesis

The current TB preventive therapy recommended by the ATS and CDC of nine months of daily INH has several shortcomings: 1) it is not remarkably effective, reducing the risk of TB by around 65%; 2) patient noncompliance somewhat reduces its efficacy; 3) 10-20% of patients taking INH may experience mild hepatic dysfunction, and 4) INH is inactive against INH-resistant strains of TB.[8] Poor patient adherence is a problem common to most long-term drug regimens, and DOT is a potential solution. DOT, however, is most feasible with regimens that are short-term and allow for intermittent dosing. Improving preventative therapy for TB involves finding short-term, intermittent drug regimens, which are proven to be at least as effective and tolerable as daily 9INH. Rifapentine (RPT) is a rifamycin derivative with a pharmacological profile that makes it a candidate for short-term, intermittent therapy. RPT/INH administered once weekly for three months has proven to be effective at preventing TB disease in infected animal models.[6, 8] **The hypothesis of this trial, Tuberculosis Trial Consortium (TBTC) Study 26, is that weekly 3RPT/INH administered under DOT will be at least as effective as daily self administered 9INH at preventing TB in high-risk individuals carrying LTBI.**

Specific Aims

The specific aims of Study 26 are to:

Primary Specific Aim:

Evaluate the effectiveness (based on intention-to-treat) of weekly 3RPT/INH vs. daily 9INH in preventing TB in high-risk tuberculin reactors.

Secondary Specific Aims:

A. Compare the tolerability and completion rates of 3INH/RPT vs. 9INH.

B. Compare the efficacy (completer-compliers) of 3INH/RPT vs. 9INH.

Significance

If 3RPT/INH proves to be as effective and well tolerated as 9INH, then 3RPT/INH will be considered a first-line regimen for the treatment of latent Mycobacterium tuberculosis infection. The 3RPT/INH will also be considered first-line regimen for LTBI if it is slightly less well tolerated but at least as effective as 9INH due to the shortened treatment period. The benefits of improved patient adherence to 3RPT/INH under DOT will boost the average effectiveness of this preventative treatment regimen, and will support the efforts made by the WHO to globally expand DOTS and control TB.

Methods

Randomization to Treatment

Approximately 3,900 subjects per treatment group will be enrolled worldwide to detect differences in TB rates and between the two regimens. Tolerability is assessed after 322 participants are enrolled in each group. Close contacts are randomized by household and all others are randomized individually. Subjects meeting inclusion criteria are randomized to receive one of the following two treatment regimens (to be started a maximum of 7 days after randomization):

Regimen 1: RPT 900mg (persons weighing ≤ 50kg take RPT 750mg) plus INH 15mg/kg (900mg max) once weekly x 12 doses (3 mos.) {DOT}

Regimen 2: INH 5mg/kg (300mg max) daily x 270 doses (9 mos.) {Self-administered}.

** 50mg Vitamin B6 will be given with each dose of INH in both study arms.

Inclusion Criteria

- The patient must be male or be a non-pregnant female ≥ 12 years old.
- At high risk for developing TB but without evidence of TB disease as determined by the principal investigator.
    1. High-risk TST reactors:
        a. Close contact (> 4 hrs in a shared airspace during a one week period) of a person with culture-confirmed, pan-susceptible TB who is TST positive (≥5

mm induration) as part of a contact investigation conducted within two years of date of enrollment.

b. TST converters- converting from a documented negative to positive TST within a two-year period. (TST $\geq$ 10 mm within two years of a nonreactive test or an increase of 10 mm induration within a two-year period).

c. HIV-seropositive, TST positive persons ($\geq$5 mm induration)

d. Persons with chest fibrosis ($\geq$ 2 cm^2 of pulmonary parenchyma fibrosis on chest X-ray) no prior history of TB treatment, TST positive ($\geq$5 mm induration) and 3 sputum cultures negative for M. tuberculosis.

2. HIV-seropositive close contact of a person with culture-confirmed TB, regardless of TST status.

- A signed informed consent, or parental consent and participant assent for children ages 12-17 is required for enrollment. A copy of the informed consent form is provided in *Appendix A*.

TST tests are read 2-3 days after administration. For HIV-negative close contacts with a negative initial TST, the TST is repeated three months later. BCG vaccination status information is not considered when reading the TST test.

HIV testing of all study patients is recommended, but not required. Documentation of HIV-seropositivity requires written documentation of a positive

ELISA and Western blot, or HIV-1 viral load ≥ 5.000 copies/ml by RT-PCR or ≥ 2,500 copies/ml by b-DNA.

Women of childbearing potential are advised to use a form of birth control if assigned to the 3RPT/INH arm. If a woman becomes pregnant while on this arm, RPT is discontinued and the woman may switch to 9INH at the investigator's discretion.

Exclusion Criteria

- Current confirmed culture-positive or clinical TB (See guidelines below)
- Suspected TB
- TB resistant to INH or RIF in the source case. If discovered after enrollment, patient is terminated from the study.
- A documented history of completing treatment for TB disease or LTBI in a person who is HIV-negative.
- Treatment > 14 consecutive days with a rifamycin, or >30 days with INH during 2 years prior to enrollment.
- Sensitivity or intolerance to INH or rifamycins
- AST or SGOT > 5x upper limit of normal
- Pregnant or nursing females
- Persons currently receiving or planning to receive anti-retroviral medications within the first 90 days after enrollment

The primary investigator should use the following guidelines to rule out active TB. A sputum culture for AFB is not necessary if the patient is asymptomatic and has a negative

chest X-ray. Patients with an abnormal chest X-ray or symptomatic HIV-infected patients with a normal chest X-ray should have negative cultures before being enrolled.

Pre-enrollment Screening

At baseline, after eligibility criteria is determined and after the informed consent form is signed, the following screening process is required:

1. A documented positive TST
2. A chest radiograph to rule out active TB obtained ≤ 90 days prior to enrollment.
3. A baseline medical history and clinical evaluation which includes:
    a. Patient demographics
    b. Height and weight
    c. Evaluation of previous treatment for TB or LTBI
    d. Evaluation of contraindications for treatment including:
        i. Confirmed or suspected TB
        ii. TB resistant to INH or rifampin in the source case
        iii. History of sensitivity or intolerance to INH or rifamycins
        iv. Current use of antiretroviral medications
        v. Current breast feeding or pregnancy

4. Evaluation for risk of liver disease (history of alcohol abuse as quantified by CAGE questionnaire, injection drug use, hepatitis, or women ≤ 3 months post-partum).

5. Laboratory Tests

    a. A pregnancy test obtained ≤ 14 days prior to enrollment of women of childbearing potential.

    b. HIV test

    c. Liver function test

Study and Follow-up Evaluations

Subsequent evaluations are conducted monthly, in person throughout the treatment periods of both regimens. The study phase evaluations include documentation of weight, symptoms of adverse drug effects, symptoms of TB, concomitant medications, new diagnoses/hospitalizations, other adverse events, and adherence to study therapy (determined by DOT records for 3INH/PT, and by pill count and interview for 9INH). In addition, if baseline AST/SGOT is above the upper limit of normal or if the patient experiences symptoms of hepatitis, liver enzyme levels are rechecked monthly during the treatment phase until normal or until symptoms cease.

Follow-up evaluations are conducted every three months until the 21-month follow-up, then every six months until study completion (33 months after enrollment). Follow-up evaluations may be done in person or over the phone. The follow-up evaluation includes assessment of weight, signs and symptoms of TB, and adverse events. If a person develops signs and symptoms of pulmonary or extrapulmonary TB, chest X-rays are performed and the appropriate specimens are obtained for culture and susceptibility testing. The schedule of study events is provided in *Table 2*.

Table 2

Schedule of Study Events

Event	Baseline	9INH Study Phase Wk 4, 8, 12, 16, 20, 24, 28, 32, 36	3INH/RPT Study Phase Week 4, 8, 12	9INH F/U Phase Month 12,15,18,21, 27,33	3INH/RPT F/U Phase Month 6, 9, 12,15,18, 21, 27, 33
Informed Consent	X				
Screening History	X				
Sputum Smear and Culture x 3 (baseline only if fibrosis on CXR) if TB symptoms	X	X	X	X	X
Offer HIV testing if HIV status unknown at baseline	X	X	X	X	X
AST(SGOT), total bilirubin, CBC w/ platelets if > 35 yrs old	X	X	X		
Pregnancy Testing	X				
Clinical Evaluation - asses TB symptoms, toxicities/AE's, concomitant medications	X	X	X	X	X
Chest Radiograph If symptoms of TB	X	X	X	X	X
Confirmation of Admin of Wkly INH/RPT			X		
Pill count		X			
Height	X				
Weight	X	X	X	X	X

Assessment of Endpoints

The study and follow-up evaluations also include assessment of endpoints. The primary endpoint of this study is the development of culture-confirmed TB in persons ≥

18 yrs old and the development of culture-confirmed or probable TB in persons < 18yrs old. Probable (clinical) Tb is defined as: Symptoms of TB (cough, fever, night sweats, weight loss, or hemoptysis) and abnormal chest X-ray PLUS either response to antituberculosis medication OR evidence of granuloma with organisms positive for AFB, or caseating granulomata at autopsy or biopsy. The study ends for patients who develop active TB.

Secondary endpoints include:

1. Development of culture-confirmed or clinical TB combined – regardless of age
2. Discontinuation of study drug permanently due to adverse drug reaction
3. Development of any grade 3 or 4 drug-related toxicity
4. Death due to any cause
5. Discontinuation of therapy for any reason (including withdrawal from study, loss to follow-up, not taking study therapy for > 3 mo.)
6. Completion of the prescribed regimen - taking 90% or more of prescribed regimen. For 3RPT/INH arm - 11/12 doses within 16 weeks

   For 9INH arm – 240/270 doses within 52 weeks
7. Resistance to study medications in isolates of M. tuberculosis from subjects who develop active TB

Subjects are followed for the entire length of the study, 33 months, even if they do not complete study therapy. Patients who fail to complete the initial course of therapy for reasons other than drug toxicity/intolerance may resume their previous regimen. They

will complete the initial course if they have taken at least 50% of the doses, otherwise they will restart the regimen.

Study Drug Toxicity Management

Patients are closely monitored in this study for signs and symptoms of study drug toxicities. The most common toxicities to INH and RPT were discussed previously. Reported toxicity symptoms are graded according the following general guidelines:

Grade 1: Mild discomfort, no limitation in activity, no medical intervention required.

Grade 2: Mild to moderate limitation in activity, no or minimal intervention required.

Grade 3: Marked limitation in activity, some assistance usually required, medical intervention required, hospitalization possible

Grade 4: Extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization possible

Grade 5: Death

For Grade 1 toxicities, the study drug is continued and the patient is closely monitored. With grade 2 toxicities, additional laboratory and/or clinic visits are conducted as necessary, and the study drug may be temporarily held at the discretion of the PI. For any grade 3 or 4 toxicity, study drugs are usually held, and other possible causes of the symptoms are ruled out. Study drugs may later be restarted or discontinued at the discretion of the PI. If drugs are discontinued, the patient will still be followed for the remainder of the study.

If the patient agrees, the PI may rechallenge the patient with individual study drugs to find the causative agent. Only grade 3 toxicities and lower should be considered for rechallenge. One week after an AE on the 3INH/RPT regimen has resolved the patient is treated with the individual drugs in this order: RPT 900 mg, B6 50 mg, INH 300 mg, INH/RPT 900 mg. If the patient is intolerant to RPT but tolerates INH, then study therapy is discontinued and the patient is put on daily INH for 9 months. If the patient tolerates RPT but not INH, then study therapy is discontinued and the patient is usually prescribed alternative (non-study) therapy of 4-6 months of rifampin 600 mg. If the patient tolerates both INH and RPT individually, but not INH/RPT together, then the patient is prescribed daily INH for 9 months. If none of the rechallenge doses are tolerated, study medicine is discontinued, and the patient is followed with chest x-rays every four months for two years. If however, the patient tolerates all rechallenge doses, the once-weekly regimen is restarted. Labs are drawn after each rechallenge if toxicity was due to lab abnormality.

If toxicity develops on the 9INH regimen, one week after the AE has resolved, the patient is rechallenged first with B6 50mg and then with INH 300mg plus B6 50mg. If the rechallenge is not tolerated, then the patient will discontinue 9INH and begin to take an alternative regimen of rifampin monotherapy. If the rechallenge is tolerated, then the regimen is continued.

*** *These methods were taken from the CDC TBTC Study 26 Protocol*

Results/Discussion

The CDC has not yet published any interim analysis of results for Study 26, most likely due to the lack of sufficient data. The enrollment goal of Study 26 is 8000 patients, however, the CDC reported at its October 2004 conference that only 3644 patients have been enrolled across the 28 participating sites. The first Study 26 participant was enrolled at the internship site, TBTC site 20, on June 5, 2001. As of September 28, 2004, over three years later, there are 710 patients enrolled in Study 26 at site 20. Only 45 of these patients though have completed the study through the 33-month follow-up. Although data from site 20 was readily accessible, there is not enough data to assess the study endpoints through statistical analysis. In this discussion, I will present a few cases and I will report percentages and trends of some of the data collected as of September 2004 from site 20; however, conclusions should not be extrapolated from this discussion.

Of the total 710 persons enrolled into Study 26 at site 20, 379 are male and 331 are female. Ages ranged from 12 to 77 years. The CDC has randomized 336 patients to the 3RPT/INH regimen, and 347 to the 9INH regimen. The other 27 are now inactive from the study. The ethnicity breakdown is 329 Hispanic, 144 African-Americans, 121 Caucasians, 106 Asians, 2 American Indians or Alaskans, 1 Native Hawaiian or Pacific Islander, and 7 other ethnicities. This study population is consistent with reported trends of foreign-born and ethnic minorities being at a higher risk of exposure to TB in the US.

This site has 531 patients in the follow-up phase and 107 patients in the treatment phase. An additional 45 patients have completed the study, and 27 withdrew consent or were withdrawn from the study. Eleven patients were withdrawn because it was

discovered after enrollment that the source case did not have culture-positive TB. Three more patients were withdrawn because the source case did not have pan-susceptible TB. Four study patients were withdrawn following protocol because they were incarcerated.

The majority of the study patients were enrolled as contacts with positive tuberculin skin tests. Converters make up the second largest classification group enrolled. Up to date, only four HIV-positive persons have been enrolled, and two of them lost eligibility and were withdrawn. Of the four HIV infected patients enrolled, one had a negative chest x-ray and a negative skin test reaction but was a contact to a case of TB, and so met eligibility criteria. As mentioned earlier, immunosuppressed persons often produce false-negative reactions to the TST test. This group is at such a high risk of contracting TB that preventative therapy is still considered. Only one subject was enrolled with evidence of fibrosis on the chest x-ray. This patient was a converter with a reported 4.0 cm^2 of fibrosis in his right upper lung. He had no symptoms of TB and had never received treatment for TB in the past. He produced three sputum specimens which all came back culture-negative; therefore, he was eligible to enroll in the study.

The primary endpoint of this study is the development of culture-confirmed TB in persons ≥ 18 yrs old and the development of culture-confirmed or probable TB in persons < 18yrs old. Thus far, none of the patients at the internship site have met the primary endpoint of Study 26. The site did enroll one patient >18 years of age who developed clinical TB during the follow-up period. This 31 year old patient was enrolled as a contact to a pan-susceptible case of TB. The patient completed nine months of INH on time and without interruptions. Two months after his 18month follow-up phone

evaluation, the patient came back from Mexico to the clinic with symptoms of a productive cough (sputum producing), chest and back pain, subjective fever, and weight-loss without dieting. He had received two penicillin shots in Mexico to treat his symptoms, however, he did not respond. The patient's chest x-ray, which was normal at baseline, showed an infiltrate in the left lung. Three sputum specimens were collected from the patient, and active TB treatment was immediately prescribed. Although five cultures came back negative, and one came back positive for *M. gordonae*, the patient responded well to antituberculosis treatment, with improvement of both symptoms and chest x-ray. The PI diagnosed this patient as a clinical case of TB meeting the secondary endpoint of the study, which is the development of culture-confirmed or clinical TB combined – regardless of age.

Another secondary endpoint of the study is discontinuation of the study drug permanently due to an adverse drug reaction. Thus far, there have 28 adverse drug reactions that resulted in discontinuation of the study drugs. Approximately 60% of these occurred on the 3RPT/INH regimen and 40% occurred on the 9INH regimen. It must be noted; however, that of the 17 patients that experienced adverse drug reactions and discontinued the 3RPT/INH regimen, the intolerable drug(s) upon rechallenge turned out to be INH in 5 patients, RPT in 4 patients, and both INH and RPT in 2 patients. The culprit drug is unknown in the other 5 patients who refused rechallenge of study drugs.

The third secondary endpoint of this study is development of any grade 3 or 4 drug-related toxicity. A total of 41 grades 3 or 4 possible, probable, or definite drug-related toxicities have been reported in the study. Only three of these were reported as

SAEs, the rest were reported as AEs. Approximately 7.7% of the patients who were randomized through this site to receive 3RPT/INH developed grade 3 or 4 drug toxicities. Toxicities on the 9INH regimen occurred at a rate of 4.3% at this site. The expected rate for both treatment regimens is about 5%. The most common toxicity related to the 3RPT/INH arm was a flu-like syndrome. This drug-related hypersensitivity reaction occurred in 13 patients on 3RPT/INH Upon rechallenge, 4 patients with flu-like syndrome were intolerant to INH, 1 was intolerant to RPT, 3 were intolerant to both, and 4 refused rechallenge. Hepatotoxicity accounted for 20% and skin rashes accounted for 27% of the total adverse drug events reported on the 9INH regimen. A flu-like syndrome similar to the one associated with the 3RPT/INH regimen was also seen in 2 patients randomized to the 9INH regimen.

Another major study endpoint is discontinuation of therapy for any reason; and this endpoint will assess adherence to treatment. Of the total number of patients who have moved past the study phase, which is 596 patients, 307 were originally randomized to 3RPT/INH and 289 to 9INH. Approximately 16.3% of the patients randomized to 9INH did not complete therapy and another 14.2% finished late. Completion of therapy on time for this regimen is defined as taking 240 out of 270 doses within 52 weeks. The most common causes of incompletion of study therapy were that the patient did not receive treatment for > 3 months (21), followed by drug related toxicity (11), refused treatment (6), and pregnancy (6). As for the 3RPT/INH regimen, only 10.4% of the patients did not complete treatment and 3.3% did not complete treatment on time, defined as 11 of 12 doses within 16 weeks. The most common causes of discontinuation of this

regimen were drug related toxicity (17), followed by refused treatment (8), failure to receive medicine for > 3 months (3), pregnancy (2), and incarceration (2).

The problem of adherence to the long 9INH regimen is seen clearly by these results. It is difficult to convince patients to take medicine for nine months when they are not experiencing any symptoms. Patients are more likely to move or change locator information during the course of nine months as well, making it more difficult to ensure they complete treatment. The 3RPT/INH regimen appears to have significantly more compliance over 9INH. It is also interesting to note that there were thrice as many pregnancies reported in the 9INH regimen compared to the 3RPT/INH regimen. This is surprising due to the fact that RPT is the drug that may interact and decrease the effects of birth control. Nine months is a far longer time to prevent pregnancy than three months. Luckily though, INH is not contraindicated in pregnant or breast-feeding women.

Overall, the preliminary data available from the internship site suggests that both treatment regimens are effective at preventing progression to active TB in high-risk persons infected with LTBI. Both regimens seem to be well tolerated although the 3RPT/INH regimen may be slightly less well tolerated than the 9INH regimen. Finally, completion rates appear to be higher in the 3RPT/INH regimen compared to the 9INH regimen. This data, however, cannot accurately assess the major endpoints of the study; therefore, conclusions should be reserved until the CDC publishes data from the entire study.

Limitations/Ethical Issues

One limitation of Study 26 is the self-report by the patient of adherence to the 9INH arm of the study and the self-report of other parameters, such as use of other medications or drugs, and side effects, which will be used to determine certain outcomes of the study. Though a limitation, self-report of adherence is by trial design. The 9INH regimen is not observed in practice and therefore will not be observed in this trial. Outreach study workers will perform pill counts and family interviews when possible to determine adherence. Another limitation is that possible bias in may result from the non-blinded nature of the study. All persons of the study team shall be committed to avoiding bias when treating, evaluating, or following-up on all study patients. Finally, due to the long length of the study period, 33 months, there may be a lower than normal completion to follow-up rate. Throughout the follow-up period, patient contact information will continually be updated to enable coordinators to keep track of study patients to their best ability.

CHAPTER III

INTERNSHIP EXPERIENCE

Internship Site Description

My 6-month internship took place at the Tarrant County Public Health Department Tuberculosis Control Clinic under the supervision of Patrick Moonan, MPH. The TCC collaborates with the research staff from the University of North Texas Health Science Center (UNTHSC), Department of Internal Medicine to conduct clinical and epidemiological studies related to tuberculosis, many of which are sponsored by the CDC. The county TB physician also serves as the principal investigator for all of the studies. Two additional co-investigators are actively involved in enrolling patients into clinical studies at the site. Individuals who are suspected to have TB or LTBI (positive TST reactors) are referred to the TCC. Two in house epidemiologists perform contact investigations in the community (including schools, businesses and nursing homes/retirement centers) in order to identify and skin test persons exposed to known cases of TB and refer them to the clinic for further diagnosis and treatment. The TCC also routinely visits the Presbyterian Night Shelter and the Tarrant county jail to test high-risk populations for TB. The population that comes into the clinic is largely foreign-born or minority, and/or of low socioeconomic status.

Eligible patients are recruited from the clinic or the PNS to participate in one or more of the studies being conducted at the site. Six clinical coordinators (including one

Spanish speaking and one Vietnamese speaking coordinator) consent and enroll patients into clinical studies. The coordinators also carry out all activities required of the study. Outreach workers assist with the study by delivering medicine or administering medicine by DOT to study patients outside the clinic. There are three major clinical studies that are actively enrolling at the internship site and several smaller ones as well.

Approximately 710 patients are enrolled into Study 26 at the internship site. Of the 28 sites around the world currently enrolling patients into Study 26, the internship site has the highest enrollment.

TBTC Study 27 is a phase II clinical trial, which is assessing the culture-conversion rates and safety of substituting moxifloxacin for ethambutol in the standard four-drug (intensive) phase of treatment for active TB. There are currently 13 patients enrolled in Study 27 at the internship site.

Also conducted at this site is a diagnostic study comparing two serological tests (QuantiFERON© and ELISPOT) to the standard Tuberculin skin test for the capacity of these tests to detect LTBI or active TB. Throughout the internship, I had the opportunity to work with each of these studies; however, most of my time was spent coordinating Study 26.

The study staff at the internship site is listed below. All members of the research team played a significant role in my learning experience.

Stephen Weis, DO – Principle Investigator

Gerry Burgess, BSN, RN – TB Program Manager

John Podgore, DO, MPH – Co-investigator

Behzad Sahbazian, DO – Co-investigator

Barbara King, BSN, RN – Clinical Research Coordinator, Supervisor

Patrick Moonan, MPH – Epidemiologist, Project Manager, On-site Mentor

Guadalupe Bayona, MD, MPH – Clinical Research Coordinator

Le Turk, RN - Clinical Research Coordinator

Norma Shafer, LVN - Clinical Research Coordinator

Gloria Stevenson, LVN - Clinical Research Coordinator

Joseph Helal, MS, RPh – Clinical Research Coordinator

Janet Marruffo, MD – Research Assistant

Sandra Small – Administrative Assistant

Patrick Pierce – Outreach Worker

Specific Aims of the Internship

As the internship progressed, I gained increasing knowledge of all aspects of coordinating a clinical trial. The following are descriptions of the key activities that I participated in during the internship. A more detailed description of my day-to-day activities during the internship can be found in *Appendix C*.

Auditing Charts and Correcting Data

A study chart is composed for each patient who is enrolled into the study. The study chart includes a copy of the signed consent form, copies of all case report forms (CRFs) sent to the CDC, and originals of all source documents necessary to support the CRFs. With the large number of patients enrolled in Study 26 at site 20, mistakes in reporting are inevitable. Thus, quality assurance is an important practice at this site.

The CDC contracts the site monitor from the clinical research organization Westat. The monitor visits the site approximately every three months, as required by the FDA. To prepare for his audit in August, another intern and I audited 110 of the most recent Study 26 charts. In this quality assurance project, 98 corrections were completed and faxed to the CDC. Omissions and/or inaccurate data found on CRFs submitted to the CDC were corrected, highlighted, and immediately faxed to the CDC. All corrections were logged and maintained in the corrections binder with proof of fax. *Table 3* is a list of the Study 26 case report forms:

Table 3

Form Number	Form Name
Form 1	Enrollment Form
Form 2	History Form
Form 3	Monthly Evaluation Form
Form 3a	Concomitant Medication Form
Form 4	Mycobacteriology Results Form
Form 5	Follow-up Evaluation Form
Form 8	Outcome of Study Therapy Phase Form
Form 9	Adverse Event Form
Form 10	Adverse Event Follow-up Form
Form 11	Development of Tuberculosis Form
Form 13	Notification of Death Form
Form 18	Study Termination/Completion Form

The most common mistakes found in the audit were omissions and transcription errors on the case report forms. To minimize the number of data errors reported to the CDC from the internship site, I developed a QA plan under the direction of the PI and the site monitor. Under this plan, all study charts are to be audited after completion of the study phase (completion of a Form 8) and again after completion of the follow-up phase (completion of a Form 18). I designed a flow sheet/checklist to follow during the quality assurance process. This QA plan is provided in *Appendix B*.

Informed Consent Process

I had the opportunity to conduct the informed consent process for Study 26 on several occasions. When informing the patient of a study, it is important to explain it in laymen terms. The purpose, randomization process, treatment regimens and potential risks and benefits of participating in the study are all addressed in the informed consent process. The patient must be ensured that participation is voluntary, quitting the study at anytime is acceptable, declining to participate will not affect his/her regular medical care, and that he/she may be removed from the study if the doctor finds it best for his/her health. The patient is given the opportunity to ask me any questions concerning study participation. After all questions are answered, I asked the patient four yes or no questions to verify understanding of the study. If the patient agrees to participate, the most recently IRB approved consent form is initialed and dated on every page, and then signed by the patient, the principal investigator, and myself. Children under the age of 18 must have a parent sign a consent form as well. It is important that each page gets initialed and dated with the correct date. The last step is to document the informed consent process in the patient's progress note.

Enrollment

After the patient consents to participate, the enrollment form (Form 1) is completed. Source documentation for pregnancy test results, skin test results, negative chest x-ray results, and baseline medical history must be collected prior to enrollment. After I collected all major source documents, I made a call to the TBTC Data Center at

the CDC to enroll the patient. The CDC data managers ask for the information entered on Form 1 to verify eligibility. Once eligibility is confirmed the CDC, assigns a study number, randomizes the patient to one of the treatment regimens and recommends dose amounts of the study drugs. The CDC ships the dosing schedule, labels, case report forms, and RPT overnight for the newly enrolled patient. After enrollment, blood is taken from the patient for a base line LFT and HIV test, and the first dose of RPT/INH is administered by DOT or the first month of INH is issued.

Administration and Accountability of Study Drugs

Patients on the 9INH regimen are issued thirty pills each of INH and pyridoxine on a monthly basis. The public health department supplies both INH and B6 locally. I issued monthly medicine at the clinic, or out in the field consistent with to the patient's preference. The dosing and evaluation schedule sent by the CDC is closely followed. At monthly evaluations the patient is weighed, evaluated for signs and symptoms of active TB, and evaluated for drug related toxicities or other adverse events. If the patient is having adverse reactions to the medicine or symptoms of TB, the symptoms are graded and the patient is referred to the clinic to see the PI. Because daily doses of INH and B6 are self-administered, I either counted the number of pills left in the bottle from the previous month, or accepted a verbal report of pills taken by the patient. I directly reported all of the information obtained from the evaluation on the source document. Later, I would transfer this information to Form 3 (Study Phase Evaluation Form) and submit it to the CDC within 14 days of the visit. A summary of each visit is also

documented in the progress note. I learned that documentation is extremely important in clinical research.

Patients randomized to the 3RPT/INH regimen receive each of their 12 weekly doses under DOT. The intervals between doses had to be > 72 hours. I administered medicine by DOT to study patients in the clinic and out in the field. Every four doses, or monthly, an evaluation similar to the one previously described is completed on patients taking 3RPT/INH and documented. The mileage I spent on delivering medicine in the field was logged and compensated for.

If scheduled evaluations were missed, a Form 3 was still sent for the missed evaluation. Similarly, if the patient came in for an unscheduled visit, a Form 3 was also sent as an unscheduled evaluation. After a patient completed or discontinued therapy, a Form 8 (Completion of Study Phase) is sent to the CDC.

Aventis provided RPT 150mg tablets in bulk. After randomization to 3RPT/INH, 72 pills were counted out of the bulk container and logged under the patients ID number. A bag containing the 72 pills was labeled with the patients name and ID number. The pharmacist designee routinely reviews the log for accuracy. Each time medicine is issued or directly observed, it must be documented on the patients dosing sheet.

Follow-up Evaluations

Follow-up evaluations were conducted according to schedule either over the phone or in person at the clinic. During the follow-up evaluation, study patients are weighed (if in person) and monitored for signs and symptoms of active TB. Patients are

also asked about adverse events that may have occurred since the last visit. If I was unable to contact a follow-up patient after several attempts, a post-master letter was delivered to the patient's address on file to verify that it is current. At each follow-up evaluation, patient contact information is updated to facilitate completion of follow-up. I issued or mailed the patient $15.00 after completion of the evaluation. A completed Form 5 (Follow-up Evaluation Form) is sent to the CDC after each completed or missed follow-up evaluation. After the 33-month evaluation, a Form 18 (Completion of Study Form) is sent to the CDC.

Because the follow-up phase is so long, almost two years, it is very hard to keep track of the patients. Patients are always moving or changing phone numbers, and finding them often requires a long investigation. However, those first two follow-up years are crucial for monitoring response to therapy and determining the major endpoint of the study, because risk of reactivation TB is greatest during that time period for most contacts and converters.

IRB Communication

There are two Institutional Review Boards with which the site must communicate. Both the local UNTHSC IRB and the CDC IRB aim to protect the human subjects on the study. When the CDC makes an amendment to the protocol or to the consent form it is delivered directly to the clinical research site. The site must submit the amended document(s) to the local UNTHSC IRB for approval. Spanish and Vietnamese versions of the consent forms are also amended and submitted for approval. Once local IRB

approval is obtained, the approved documents are then sent to the CDC IRB with proof of local IRB amendment approval. After the local IRB and the CDC IRB have both approved the amended document(s), they are stamped and dated for use. One old version of the consent form or protocol is kept in the regulatory binder for reference. All others are expired and thrown out.

I helped complete and submit local IRB continuing reviews for Studies 26 and 27. Continuing reviews are completed annually for each study. The information reported on the continuing review is pulled from the study charts or from the computer database. Before the Study 26 continuing review was submitted, another intern and I audited the computer database of Study 26 patients, which contained 730 patients, to ensure the queries turn up accurate results. Data from the queries are reported in the annual continuing reviews. Continuing reviews had to be submitted to the IRB within thirty days after they were issued.

My experiences with the IRB have taught me the importance of promptly and accurately responding to their requests. The sole purpose of the IRB is to protect the study subjects; therefore, the IRB has the eligible power to shut down a study site if there is reasonable cause. Documentation of all interactions with the IRB is imperative to prevent this event from occurring.

AE and SAE Reporting

The UNTHSC IRB requires a report of all SAEs that occur throughout the entire study. The initial report is in the form of a brief email sent within 24 hours of

occurrence. An SAE is defined by the local IRB as any experience, study drug related or not, that is fatal or life-threatening, is permanently disabling, requires or prolongs impatient hospitalization, or results in a congenital anomaly/birth defect. A subsequent detailed written report (IRB Form 3a) along with supporting documents is also requested by the UNTHSC IRB within 10 working days. All pregnancies are also reported in this manner. Follow-up reports are sent to the IRB to provide outcome information of the SAEs, such as the delivery of a healthy baby.

The CDC IRB has different reporting requirements. The CDC expects a Form 9 (Adverse Event Form) and a Form10 (Adverse Event Follow-up Form) for each reportable AE and all SAEs that occur during treatment or within 60 days after completion of therapy. AEs or SAEs that occur after this time bracket are not reported to the CDC. Form 9 is the initial report and is requested by the CDC within 48 hrs of notification of the event if it is a serious adverse event related to study therapy, or as soon as possible if otherwise. The CDC defines SAEs in the same way they are defined by the local IRB. A reportable AE, as defined by the CDC, includes events resulting in permanent discontinuation of study therapy, new medical diagnosis, grade 3 or 4 toxicity, incorrectly administered study therapy, pregnancy, and persisting methadone withdrawal symptoms. All events that fit in these criteria are reported and graded whether they are study drug related or not. Form 10 is the follow –up report to the SAE and is sent within 45 days, or after resolution of the AE or SAE.

Maintaining Regulatory Binders

One or more regulatory notebooks are maintained for each ongoing study at the internship site. The FDA requires maintenance of these binders. The following documents are required to be present and updated in the regulatory binder(s):

- Copy of the current version of protocol
- IRB approval of protocol
- IRB approval of amendments
- IRB approved consent forms accompanied by the approval letters from both IRBs
- Continuing Reviews
- Safety Reports
- Form FDA 1572 (List of key study personnel) plus CVs of study staff
- Laboratory certification
- IRB correspondence documents
- Investigator's Brochure
- Drug accountability records

By the conclusion of the internship I was completing all activities required of a clinical coordinator at the site. The skills I acquired from the internship will be extremely valuable in my future clinical research endeavors.

APPENDIX A

STUDY 26 CONSENT FORM

INFORMED CONSENT AUTHORIZATION
FOR PERSONS 18 YEARS OF AGE AND OLDER
TO TAKE PART IN A RESEARCH STUDY

TITLE: **A Study of the Effectiveness and Tolerability of Weekly Isoniazid and Rifapentine for Three Months vs. Daily Isoniazid for Nine Months for the Treatment of Latent Tuberculosis Infection**

Centers for Disease Control and Prevention

INSTITUTION: University of North Texas Health Science Center at Fort Worth

PRINCIPAL INVESTIGATOR: Stephen E. Weis, D.O.

SUBJECT NAME (Please Print):

_____

Before agreeing to take part in this study, it is important to carefully read the following explanation of the intended procedures. This consent form may contain words that you do not understand. Ask the study doctor or the study staff to explain any word or information that is not clear to you. Also, understand that if you decide not to take part in this study, your treatment will not be affected and there are other drugs available for the treatment of your symptoms.

If you are a student or employee at the University of North Texas Health Science Center at Fort Worth, your participation (or non-participation) will in no way affect your academic standing or employment status.

I. STUDY PURPOSE

This is a clinical trial (a type of research study). Clinical trials only include patients who choose to take part. Please take time to make your decision. Discuss it with your family and friends.

You are being asked to be in this study because you have the germ that causes tuberculosis (TB). This is called having latent TB infection. People with latent TB infection can develop TB disease. TB is a bacterial infection that usually results in a serious lung disorder. The University of North Texas Health Science Center at Fort Worth and the Centers for Disease Control and Prevention (CDC) are working together on this study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out whether taking 3 months of rifapentine and isoniazid (INH) works as well as taking 9 months of INH, the commonly used treatment. The study will also see what side effects are caused by taking rifapentine and INH for 3 months.

Medicine can get rid of the germs that give a person latent TB infection. This keeps the person from getting TB disease. Usually people with TB infection take *one* drug, INH. They have to take it every day for 9 months. In this study, half of the people enrolled will take *two* drugs, rifapentine and INH, but only once a week for 3 months. We think this will work as well as 9 months of daily INH. The main purpose of this study is to compare the ability of these two treatment options to prevent the development of active tuberculosis.

Rifapentine has been tested as a cure for TB disease. The tests showed that it works and is safe. Because of this, it was approved by the Food and Drug Administration (FDA). But it hasn't been tested as a cure for latent TB infection. The amounts of rifapentine we are using in this study (750-900 mg) are higher than what the FDA approved (600 mg). However, these higher doses were safe and well-tolerated when tested in earlier studies.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 8,000 people will be in this study and enrollment into the study will take over 5 years.

HOW LONG WILL MY PARTICIPATION IN THE STUDY BE?

We expect that you will be in the study for 33 months (2 years + 9 mos.)

COSTS AND COMPENSATION FOR BEING IN THE STUDY.

There is no cost to you for being in the study. You will not have to pay for any medicine or tests that are part of this study.

You will receive $15.00 per completed *follow-up* visit as compensation for your time and travel expenses in this study. As applicable, reimbursement to you may be withheld and credited to any outstanding debts you may have with the University of North Texas Health Science Center at Fort Worth or the State of Texas.

I. STUDY PROCEDURES

WHAT IS INVOLVED IN THE STUDY?

Enrollment. If you enroll in the study, you can expect the following:
You will be assigned to a treatment group by chance (like flipping a coin). Neither you nor the research doctor will choose which group you are in. The treatment groups to which you might be assigned are either:

- rifapentine and INH once a week for 3 months

OR

- INH every day for 9 months

Others in your household may be eligible and agree to be in this study. If so, they will be assigned to the same treatment group and receive the same medicine as you.

You will be given a chest x-ray (unless you had one recently). This is to make sure you don't have TB disease in your lungs. If you take medicine for latent TB infection when you actually have TB disease, you could get sick.

You will be asked questions about your health like any past treatment for TB or latent TB infection, and medicines you are taking. We will ask about any other illnesses and if you drink or take drugs.

You will be asked if you have HIV infection. If you have not had an HIV test ever, or if it's been a while, we think you should have one. We can give confidential HIV testing and counseling. However, you do not have to have an HIV test to be in this study. If you are HIV positive, we need to have a copy of your HIV-positive test results for this study. Also, if you are HIV positive, we want to get a copy of your most recent CD4 count. We will ask you to sign a medical release form so we can get this lab result from the doctor, clinic or hospital that did it.

Some people in the study will have about 2 teaspoons (10 cc) of blood drawn from a vein. We will use this blood test to check the liver and blood if you: a) Are among the first 644

persons enrolled in the study. b) Have risk for liver disease. c) Have had a baby 3 months ago or less. d) Are HIV positive.

If you can get pregnant, we will do a pregnancy test.

Treatment. The treatment phase of the study is the time while you're taking medicine. During this time you will have the following tests and procedures:

If you take rifapentine and INH, a health care worker will meet with you each week to give you the medicine.

If you take INH daily for 9 months, you will take the medicine every day on your own. Someone may watch you take the medicine, but it would not be a health care worker from the study.

If you are HIV-positive: You can't take certain HIV medications for the first 90 days that you take medicine for latent TB. These are drugs like amprenavir (Agenerase), indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), lopinavir and ritonavir combination (Kaletra), saquinavir (Fortovase), efavirenz (Sustiva), nevirapine (Viramune), and delavirdine (Rescriptor). You and your HIV doctor will decide together if this is an appropriate thing for you to do. If you enroll and take rifapentine, you will need to wait at least 7 days after the last dose of rifapentine before starting to take any of the HIV medicines listed above.

You will meet with a study doctor or nurse once a month. The meetings will take about 20 minutes. At the meetings:

- We will ask if you have had any side effects from the medicine or symptoms of TB.
- We will ask you about any medicines you have taken and any illness you have had since we last met. If you are taking methadone we will ask about symptoms of methadone withdrawal.
- If you take INH alone, we will refill your monthly supply of INH. We will count any left over medicine. We will ask you how often you took (or forgot to take) your INH.
- If the blood test of your liver was abnormal at the start of the study, you will have about 1 teaspoon (5 cc) of blood drawn to check your liver after one month of treatment.
- If you have symptoms of problems, you will have about 2 teaspoons (10 cc) of blood drawn to check your liver and blood count.
- If at any time you develop symptoms of TB, you will have a chest x-ray and an exam of your sputum (phlegm coughed up from your lungs).

We will stop the study medicine if you have bad side effects, or if the study ends sooner than planned. Even if the study medicine is stopped, we will still follow you in the study. If you get active TB, your part in the study stops. If you are incarcerated (jailed) prior to enrollment, you are not eligible to take part in this study. If you are incarcerated during the treatment phase of the study, you will be withdrawn from the study and you will no longer be given study medicine. If you are withdrawn, the study doctor will refer you for different treatment, but you will continue to receive medical care.

Follow-up. This part of the study starts when you finish taking the medicine. If you took rifapentine and INH once a week, we will keep in contact with you for 2 ½ years after your treatment ends. If you took INH every day for 9 months, we will keep in contact with you for 2 years after your treatment ends. The total length of time both treatment groups will be in the study is 33 months. Even if you stopped the medicine early, you will still be tracked for the study.

During this follow-up,

- We will keep in contact with you after you finish the medicine. We will ask you questions about your health every 3 months (4 times/year) until you have been in the study almost two years, then twice during the last year of the study. You can answer these questions over the phone or at the clinic.
- If you get symptoms or signs of active TB, we will see you at the clinic for a medical visit. You will get a chest x-ray and sputum exam.
- You will come in to the clinic for one final visit. The last visit must be in person. This visit is very important for you, to make sure that the medicine you took kept you from getting active TB. The visit is important for us, to make sure we have the results for our research study.
- If you move away while you are in the study, we will still continue to follow you. If we cannot see you in person, we will contact your new doctor or clinic, or the health department in your area, for help in carrying out study visits. The study visits will be the same as described in this consent form. Dr. Weis will continue to be in charge of the study work in your new location.
- If you are in prison or jail while you are in the follow-up phase of the study, we will still continue to follow you, however, you will not receive study medicine. If we cannot see you in person, we will contact the medical staff at the facility where you might be, for help in carrying out study visits. The study visits will be the same as described in this consent form. Dr. Weis will continue to be in charge of the study work even if you are incarcerated (jailed) during the follow-up phase of the study.

III. RISKS AND DISCOMFORTS OF THE STUDY

WHAT ARE THE RISKS OF THE STUDY?

Possible side effects from the study drugs include the following:

- INH can cause the nerves in the hands and feet to tingle or lose feeling. However, this is not likely at the dose you will get. You may be given vitamin B6 with INH to lower the risk of the nerve problem.
- Although not frequent (it happens in less than 1 % of persons), the most serious side effects from INH is liver damage (hepatitis) and jaundice (yellow skin and/or eyes). The symptoms of this include nausea, loss of appetite, pain in the right side of your abdominal area, and dark colored urine. If any of these symptoms occur, you should immediately stop taking your medicines and let us know, so we can evaluate you at the clinic. Very rarely, this can be fatal. Rifapentine can also cause this side effect, but the risk of this side effect is less than with INH.
- Rifapentine can make your tears, sweat, saliva, feces, and urine turn orange. Contact lenses may be stained forever due to the orange color of your tears.
- Rifapentine and INH can make the number of platelets drop. Platelets are a type of blood cell that help blood clot. If the number of platelets is very low, this can cause a bleeding problem and may cause purple spots on the skin. This side effect is rare (less than 1%) but potentially serious, and you need to call your doctor or study nurse immediately if this problem develops.
- Both INH and rifapentine can cause itching, rash, fever, feeling sick to your stomach, heartburn, reduced appetite, nausea, vomiting or diarrhea. Both INH and rifapentine can cause headache, dizziness, weakness, joint pain, anemia, and low white blood cells. Most people who take these medicines do not get these problems.
- INH can also cause low vitamin levels, high blood sugar, seizures, altered consciousness (awareness), visual disturbances, memory loss, and psychosis (severe mental disorder). Rifapentine may also cause blood in the urine and reduced kidney function. Again, most people who take these medicines do not get these problems.
- Both INH and rifapentine can cause other medicines that you take to not work right. Please tell your study nurse or doctor before you start any other medicine during the time you are taking INH or rifapentine. This includes even over-the-counter medicine such as antacids, Tylenol, etc.
- Although not frequent (to date, it has been reported in less than 1% of persons in this study), taking both INH and rifapentine can make you feel like you have the flu. The symptoms of this include fever, chills, sweats, body aches, and red eyes and warm skin. The more severe but more rare symptoms of this also include fainting, a drop in blood pressure and a drop in body temperature.

This reaction to the drugs could be serious, and you need to call your doctor or study nurse if it develops.

There may be other side effects from these medicines that we don't know about yet.

We estimate that the two treatment groups in the study will have about the same risk for side effects. If you have side effects you ***must*** tell your study doctor or nurse right away. If that happens you will be evaluated and told what to do. For serious side effects you might have some blood tests. You may be taken off the study medicine. Your doctor will then decide if you should re-start your medicine or not.

There are a few small risks from having blood drawn. These include brief pain from the needle stick, bruising, bleeding, lightheadedness, and rarely, infection where the needle enters the vein.

You might feel that some of the questions we ask as part of the study are too private. You do not have to answer these questions if you do not want to.

INFORMATION JUST FOR WOMEN

INH does not appear to cause birth defects. However, we don't know how safe rifapentine is for pregnant women or women who are breastfeeding their child. Therefore, you will not be allowed to take part in this study if you are now pregnant, plan to become pregnant before completing your treatment, or breastfeeding. You will get a pregnancy test before starting treatment if you can get pregnant.

In addition, rifapentine can make birth control pills, hormone injections, and implants not work for the prevention of pregnancy. If you take rifapentine and INH, you should use some other kind of birth control (such as condoms, diaphragms, sponges, cervical caps, or intrauterine devices [IUDs]).

If you become pregnant you ***must*** tell your study doctor or nurse right away. If that happens, you may be taken off the study medicine. Your doctor will then decide which treatment is right for you and your baby.

IV. CONTACTS

If a study-related problem should occur or you experience an adverse reaction, or if you have any questions at any time about the study, you may contact Dr. Weis' office at (817) 735-2660 (please identify yourself as a research study patient). If you have any questions about your rights as a participant in this research study, you may contact Dr. Jerry McGill, Chairman, Institutional Review Board, University of North Texas Health Science Center at Fort Worth at (817) 735-5483 for more information.

V. BENEFITS

There are no direct benefits for you for taking part in this study except that you will receive treatment to prevent active TB. Your taking part in this research will help us learn more about how to treat latent TB infection.

VI. ALTERNATIVE TREATMENTS

If you choose not to take part in this study, there are several recommendations for treatment:

- CDC recommends INH daily for 9 months as the best treatment.
- CDC also recommends rifampin and pyrazinamide (PZA) daily for 2 months (instead of INH), especially for persons with HIV.

You can decide to not take medicine, but that will increase your risk of getting TB disease.

The health department or your doctor can give you information about other recommended treatment.

VII. CONFIDENTIALITY

We will check your medical records to get information for the study. We will not use your name in any speech or paper about the study. We will not send your name to the study's data center (CDC). The FDA, study monitors from CDC, and the University of North Texas Health Science Center Institutional Review Board (UNTHSC IRB) may also check your records. We will keep all information from your medical records private as much as the law allows.

VIII. COMPENSATION FOR INJURY

If you believe that you have a research-related injury, further information concerning the availability of treatment can be obtained from Dr. Weis at (817) 735-2660.

Neither the research doctor conducting this study, the Centers for Disease Control and Prevention (CDC), nor the University of North Texas Health Science Center at Fort Worth are able to offer compensation nor to absorb the costs of medical treatment should you be injured as a result of your participation in this research. If required, medical care will be made available to you in the case of injury, but you (or your private insurer, Medicare, Medicaid or other governmental healthcare program) will be responsible for the expense of any medical care, including hospitalization, that is needed.

You should know that by signing this form, you are neither waiving any of your legal rights against nor releasing the CDC, the research doctor, the University of North Texas Health Science Center at Fort Worth or any of their respective agents from liability for negligence with respect to the conduct of this study. If you are injured and feel that your injury justifies pursuing a legal remedy, you have the right to do so.

IX. LEAVING THE STUDY

Taking part in this study is voluntary. If you choose not to take part, it will not change your regular medical care. If you choose to be in the study, you may quit at any time without changing your regular medical care. Your doctor could also remove you from the study if he or she felt that it was best for your health to do so. Your doctor will discuss this with you.

X. NEW FINDINGS

If important new findings develop that may affect your willingness to continue your participation in this study, you will be told as soon as possible so you can decide whether to continue your participation or withdraw from the study.

XI. CONSENT

I voluntarily consent to take part in this study. I have read and understand this statement of informed consent and the risks described. I understand that I may withdraw my consent or withdraw from this study at any time without losing any benefits I otherwise would have. I have had all alternative treatments discussed with me.

I HAVE RECIVED A COPY OF THIS SIGNED INFORMED CONSENT AGREEMENT

Subject Name (print)	Signature	Date
Legal Representative [if applicable] (print)	Signature	Date
Person who conducted Informed Consent discussion (print)	Signature	Date
Witness (print)	Signature	Date

APPENDIX B

QUALITY ASSURANCE PLAN

QUALITY ASSURANCE PLAN FOR STUDY 26
AT SITE 20

All Study 26 charts shall be quality assured after a Form 8 is completed and after a Form 18 is completed. The following is a guide for quality assuring Study 26 charts.

After FORM 8 is complete:

Source Documents
☐ IC signed and dated
☐ Consent process documented in clinic note
☐ Doctor's dictation signed and filed
☐ Laboratory Results graded and filed
☐ HIV result filed
☐ Pregnancy test result filed
☐ Interview sheet complete and filed
☐ TB-400 completed, signed, and filed
☐ Case susceptibility documented in dictation or clinic note
☐ Client visit record for each scheduled/missed/unscheduled visit
** *describe all symptoms*
☐ New TB-400B for patients on Alt. Meds. – *reported in database -sticker*
☐ Source documents to support AEs/SAEs
☐ Dictation for Form 8

Case Report Forms (should match source documents)
☐ Enrollment form matches SD
☐ History form matches SD
☐ Laboratory Report Form at enrollment and when blood drawn
☐ Concomitant Medication Form at enrollment and if meds change
☐ Monthly Evaluation Form for each scheduled/missed/unscheduled visit
☐ Form 8 complete * *if patient withdrawn/withdrew report in database*
☐ AE/SAE forms and F/Us complete and *reported in database*

☐ Send corrections
☐ Put a green sticker on study chart
☐ QA computer database

After FORM 18 is complete:

Source Documents

☐ IC signed and dated
☐ Consent process documented in clinic note
☐ Doctor's dictation signed and filed
☐ Laboratory Results graded and filed
☐ HIV result filed
☐ Pregnancy test result filed
☐ Interview sheet complete and filed
☐ TB-400 completed, signed, and filed
☐ Case susceptibility documented in dictation or clinic note
☐ Client visit record for each scheduled/missed/unscheduled visit
** *describe all symptoms*
☐ New TB-400B for patients on Alt. Meds. – *reported in database*
☐ Source documents to support AEs/SAEs
☐ Dictation for Form 8
☐ Follow-up visit records for all scheduled/missed/unscheduled F/Us
☐ Dictation for Form 18

Case Report Forms (should match source documents)

☐ Enrollment form matches SD
☐ History form matches SD
☐ Laboratory Report Form at enrollment and when blood drawn
☐ Concomitant Medication Form at enrollment and if meds change
☐ Monthly Evaluation Form for each scheduled/missed/unscheduled visit
☐ Form 8 complete * *if patient withdrawn/withdrew report in database*
☐ AE/SAE forms and F/Us complete and *reported in database*
☐ F/U evaluation forms for each scheduled/missed/unscheduled follow -up
☐ Form 18 complete and signed

☐ Add orange sticker
☐ Send corrections
☐ QA computer databases

APPENDIX C

INTERNSHIP JOURNAL OF DAILY ACTIVITIES

INTERNSHIP JOURNAL OF DAILY ACTIVITIES

May 24, 2004 – October 28, 2004

Week 1

Monday, May 24, 2004

First day of internship. Began watching a series of videos on tuberculosis. Completed the first two modules, an introduction to TB and epidemiology of tuberculosis.

Tuesday, May 25, 2004

Reviewed modules three and four covering evaluation and diagnosis of tuberculosis infection and disease and treatment of LTBI and TB disease.

Wednesday, May 26, 2004

Completed modules 5 and 6 on infection control and contact investigations.

Thursday, May 27, 2004

Completed module seven on confidentiality in TB control. Sat in on Dr. Weis's afternoon clinic.

Friday, May 28, 2004

Completed modules 8 and 9 on TB surveillance and management in hospitals and institutions, and on adherence to TB treatment.

Week 2

Monday, May 31, 2004

Memorial Day.

Tuesday, June 1, 2004

Completed Module 9 and sat in on Dr. Weis's afternoon clinic. Got TB skin tested.

Wednesday, June 2, 2004

Spent a few hours pulling articles from the clinics resources. Met with one of the clinical research coordinators who trained me how to fill out case report forms from source documents, assemble the study chart, and enter newly enrolled study participants into the computer database.

Thursday, June 3, 2004

In the morning, I helped a coordinator correct source documents sent back to the clinic by the CDC. In the afternoon I sat in on Dr. Weis's clinic. I also got my skin test read and it was negative.

Friday, June 4, 2004

Today I passed the quiz covering the TB modules that I have spent the last two weeks reviewing.

Week 3

Monday, June 7, 2004

Observed Patrick Moonan consent patients, draw blood, and administer TST for the QuantiFERON© clinical trial. After consenting and enrolling three patients we watched him prepare blood-antigen solutions for each patient to be incubated and sent off to an out-of-state lab.

Tuesday, June 8, 2004

I watched a CD-ROM on the shipping of hazardous materials and then took the quiz to be certified. I then spent the afternoon filling out Form 3 for several Study 26 patients.

Wednesday, June 9, 2004

Filled out CRF's for Study 26, and assembled study charts. Quality assured completed CRF's to be sent to the CDC. Updated regulatory binders with the recently amended protocol and consent forms. Shredded old consent forms and replaced them with updated ones.

Thursday, June 10, 2004

Worked on research proposal. Filled out CRFs and quality assured them.

Friday, June 11, 2004

I worked on my research proposal all day.

Week 4

Monday, June 14, 2004

Today I filled out case report forms for lab results, monthly evaluations, concomitant medications, and histories. I also fixed corrections on returned CRFs and faxed them back to the CDC.

Tuesday, June 15, 2004

I designed a source document which would ensure sufficient information intake in order to complete the CRF for the Continuation Treatment Phase of Study 27. Completed several case report forms for Study 26. Filed progress notes in study charts.

Wednesday. June 16, 2004

I designed another source document for Study 27, but this one was to correspond with the CRF for the Intensive Treatment Phase Evaluation. I continued to fill out Study 26 CRFs. In addition I filed outreach forms and progress notes into study charts.

Thursday, June 17, 2004

I designed a template for reporting serious adverse events to the UNTHSC IRB and showed one of the coordinators how to use it. I completed CRFs and filed progress notes.

Friday, June 18, 2004

Out of office to observe ex-President Ronald Regan's death.

Week 5

Monday, June 21, 2004

Completed and sent enrollment forms, history forms, lab forms, and monthly evaluation forms to the CDC. I quality assured the charts as I completed the forms for Study 26.

Tuesday, June 22, 2004

Today I accompanied a CSA worker all morning as he delivered study medications in the field. In the afternoon I completed and QAd approximately several CRFs for Study 26.

Wednesday, June 23, 2004

In the morning I accompanied Le Turk on a home visit to deliver Study 26 medications. In the afternoon I completed and corrected Study 26 CRFs.

Thursday, June 24, 2004

This morning I helped Le Turk, RN, CRC enroll a patient into Study 26. I observed her conduct the consent process, take of the participant's history, and draw the patient's blood for liver function tests and HIV tests. I then proceeded to complete the enrollment form and fax it to the CDC. I assembled the study chart for this patient as well.

Friday, June 25, 2004

I filed labs and completed about several laboratory CRFs for Study 26. I practiced taking blood on two of the coordinators.

Week 6

Monday, June 28, 2004

I filed progress reports in the morning. I then designed a source document for Study 24. In the afternoon I completed and QAd Study 26 CRFs.

Tuesday, June 29, 2004

Assisted Dr. Bayona with a Study 26 monthly evaluation at the clinic and completed the source document and Form 3 for this patient. I reviewed the contents of the various regulatory binders at the clinic. Patrick Moonan helped me to understand the statistical analysis described in the Study 26 protocol for reference in my research proposal.

Wednesday, June 30, 2004

This morning I attended my advisory committee meeting to discuss and approve my research proposal. After the meeting I went to the library to work on a few corrections they asked me to make.

Thursday, July 1, 2004

I filled out lab CRFs. I made a couple follow-up evaluation phone calls to Study 26 patients. I completed an online course and passed a test on conducting research with experimental subjects.

Friday, July 2, 2004

Completed my research proposal, obtained committee signatures, and submitted my research proposal to the graduate office.

Week 7

Monday, July 5, 2004

Observed holiday for the Forth of July.

Tuesday, July 6, 2004

Out of office.

Wednesday, July 7, 2004

I filed progress notes for an hour. I completed Study 26 monthly evaluation forms and follow-up evaluation forms. I took the HIPPA certification test at UNTHSC library. .

Thursday, July 8, 2004

Discussed AEs and SAEs with Dr. Bayona, CRC. Assembled study binders and completed enrollment forms for two patients. I assisted Dr. Bayona with enrolling two patients.

Friday, July 9, 2004

Attended a meeting of the clinical research staff and Dr. Weis, PI in the morning. In the afternoon, I enrolled two patients into Study 26 by calling the CDC to randomize them to a treatment arm. I then proceeded to assemble their study charts, fill out enrollment and concomitant medication CRFs, and enter the new profiles into the computer database.

Week 8

Monday, July 12, 2004

This morning I helped enroll a new patient into Study 26. I called the CDC to randomize the patient. I also assisted with a monthly evaluation. After lunch, Le Turk, RN, CRC showed me how to fill out adverse event CRFs.

Tuesday, July 13, 2004

This morning I helped collect and review all 9 of the Study 27 charts in order to complete a continuing review of this study for the local UNTHSC IRB. In the afternoon I filed progress reports and labs. I also designed and updated a patient spreadsheet for Study 27.

Wednesday, July 14, 2004

This morning I called the CDC and enrolled two patients into Study 26. I QAd CRFs to be mailed to the CDC and completed CRFs for Study 26.

Thursday, July 15, 2004

This morning I filed lab results and progress notes. I QAd CRFs to be sent to the CDC. I worked on corrections and faxed them back to the CDC. I also accompanied Dr. Bayona, CRC on a home visit to deliver study medications.

Friday, July 16, 2004

I reformatted and updated the Study 26 refusal/ enrollment list required by the CDC. I also did follow up evaluation on a Study 26 patient. Then I enrolled a patient into Study 26. I helped Dr. Bayona make necessary changes to the Spanish version of the Study 26 consent forms. These documents will be sent to the IRB for approval.

Week 9

Monday, July 19, 2004

I continued to update the Study 26 refusal list from September 2003 enrollments/refusals till the present. I enrolled a patient in to Study 26.

Tuesday, July 20, 2004

I completed Study 26 labs and history forms. I did a follow-up phone evaluation and completed the F/U CRF. I pulled study charts of participants eligible for sub-study 26A to see if they can still be enrolled. I QAd a few study charts.

Wednesday, July 21, 2004

Today I consented my first Study 26 participant. I assisted with the collection of the necessary specimens for lab tests – pregnancy, liver function, and HIV. I then enrolled the patient into Study 26 and administered the first dose of medicine by DOT. I was very excited to enter my first patient into Study 26 on my own. I completed updating the refusal list and printed off a copy for the regulatory binder.

Thursday, July 22, 2004

I filed progress reports and completed CRFs for Study 26. I also filled out outcome of therapy forms and made sure they were signed and dictated by Dr. Weis. I completed 26A enrollment forms and updated the Study 26A enrollment datasheet.

Friday, July 23, 2004

Today I went with Patrick Moonan to White Settlement Nursing Home to draw blood for for the QuantiFERON© study. I assisted with the blood draw, and interviewed the patients.

Week 10

Monday, July 26, 2004

I filed progress reports and filled out lab forms for two hours. I then called the CDC to enroll/refuse patients chosen to be controls for sub-study 26A. After lunch, I enrolled a patient into Study 26 and assembled study charts for two more newly enrolled patients. I updated the 26A roster and assembled refusal charts for the 26A controls I had called the CDC on earlier.

Tuesday, July 27, 2004

I filed progress notes and labs. I completed history forms and form 8 for Study 26. Worked with approximately 15 charts today, QAing them in the process.

Wednesday, July 28, 2004

I printed off a list of missing treatment evaluations for Study 26 and began investigating charts on the list to find out if the patient had completed therapy or needs more medicine. I went to the Vietnamese Temple with one of the coordinators to help draw blood and evaluate four Study 26 patients. After, I filled out evaluation forms for these patients.

Thursday, July 29, 2004

Today I worked with 12 charts, completing history forms, lab forms, monthly evaluation forms and outcome of therapy forms. I also QAd 20 case report forms.

Friday, July 30, 2004

I worked with two charts in the morning and completed appropriate forms. I then helped the research assistant organize the list of follow-up patients. Next week we will separate charts on treatment from charts on follow-up.

Week 11

Monday, August 2, 2004

Out sick.

Tuesday, August 3, 2004

Completed laboratory report forms and filed progress notes. Quality assured case report forms to be sent to the CDC. Completed corrections to Study 26 case report forms.

Wednesday, August 4, 2004

Quality assured Study 26 charts in the morning and completed corrections. In the afternoon I went through the layout of Study 27 study charts and learned when specific case report forms are required to be sent. Then I quality assured one Study 27 chart, and sent six corrections on this chart.

Thursday, August 5, 2004

I QAd Study 26 and 27 charts, completed appropriate corrections and faxed them to the CDC. I also filed source documents and made corrections to case report forms sent back by the CDC.

Friday, August 6, 2004

I QAd three Study 26 charts. I enrolled one patient into Study 26. I met with my mentor, Dr. Gwirtz to discuss my internship and my final thesis. After lunch I helped Patrick update QuantiFERON© case report forms.

Week 12

Monday, August 9, 2004

I QA'd five Study 26 charts and faxed corrections to the CDC. I helped with an IRB continuing review for Study 27 sub-study NAA. I also filed source documents and completed laboratory report forms.

Tuesday, August 10, 2004

I QA'd Study 26 charts and faxed corrections to the CDC. We are preparing for an audit by the monitor. I also made corrections to several case report forms sent back by the CDC.

Wednesday, August 11, 2004

I obtained consent from one patient today and enrolled two more patients into Study 26. I prepared charts for these patients and sent appropriate forms. I QAd 3 charts as well and faxed corrections to the CDC.

Thursday, August 12, 2004

QAd charts in the morning. I then made a trip to the UNTHSC IRB to drop off an SAE report. In the afternoon I obtained consent from two more patients and assisted Dr. Bayona with another one.

Friday, August 13, 2004

I enrolled two patients into Study 26 who signed the consent the night before. I QA'd charts and sent corrections. I prepared Study charts for new enrollees. I also helped Le Turk update her charts.

Week 13

Monday, August 16, 2004

I helped Le Turk update charts by filling out case report forms and updating evaluation dates in the computer database. After lunch I enrolled three new Study 26 participants, prepped their charts, and completed appropriate case report forms. I also completed two corrections.

Tuesday, August 17, 2004

In the morning I filled out case report forms and pulled charts to be QAd for the audit next week. I delivered study medicine to two patients and updated their charts.

Wednesday, August 18, 2004

In the morning I updated charts from the previous day's deliveries and evaluations. I QAd several charts. I delivered medicine to three patients in the afternoon.

Thursday, August 19, 2004

I enrolled two patients in the morning. I delivered medicine at lunch. I QAd three charts after lunch and filled out case report forms. I completed corrections on the charts I QAd.

Friday, August 20, 2004

I QAd charts in the morning and completed a few lab forms. I left after lunch to work on my thesis.

Saturday, August 21, 2004

Delivered medicine and DOTd one Study 26 patient.

Week 14

Monday, August 22, 2004

I updated the Study 26 charts and screening log/refusal list. I pulled all of the charts in which Bert Arevalo, site monitor from Westat, will be auditing tomorrow and balanced the drug accountability log for the Study 26 drug, rifapentine.

Tuesday, August 23, 2004

I also went through the drug accountability log with a coordinator again to make sure it balances. I then designed a spreadsheet on excel to keep the log updated and balanced in the future. Bert went through the charts he audited today with another intern and I so that we could correct mistakes he found and prevent future errors.

Wednesday, August 24, 2004

I shadowed Bert Alevaro, study monitor, for a while. In the afternoon, I helped Dr. Bayona update charts. I enrolled one patient into Study 26 and completed her paperwork.

Thursday, August 25, 2004

I prepared charts for four new patients who consented to participate into Study 26. I went to lunch with Bert to discuss and learn more about what he does as a monitor. Later I enrolled the four patients mentioned above.

Friday, August 26, 2004

I delivered medicine to a Study 27 patient. Bert had his exit meeting with the entire clinical research staff. After the meeting, I finished updating new enrollees into the ,

Saturday, August 27, 2004

I delivered medicine and DOTd one Study 26 patient.

Week 15

Monday, August 29, 2004

This morning I enrolled one patient into Study 26, assembled her chart, and will deliver her medicine after work. I completed history forms and one concomitant medication form. I helped Le fix the template spreadsheet she uses for recording her weekly statistics. After lunch I completed a follow-up evaluation and gathered data for my thesis.

Tuesday, August 30, 2004

This morning I completed history forms and laboratory report forms for study patients. I then worked on corrections pointed out by Bert during the audit. Another intern and I made a list of the most common mistakes based on what we found when we QAd charts and what Bert found in his audit. After lunch I left to work on my thesis.

Wednesday, August 31, 2004

I worked with several Study 26 charts completing CRFs. I also did some research to find out how many charts were QAd to prepare for the audit, and how many corrections were made to those charts. I will report the results in my thesis.

Thursday, September 1, 2004

In the morning I completed evaluation forms and outcome of therapy forms. After lunch, I read the Manual of Operating Procedures for Study 26 to review for my thesis.

Friday, September 2, 2004

I helped Le update five Study 26 charts. We completed monthly evaluation and outcome of therapy forms. After lunch I filed progress reports and outcome of therapy forms that Dr. Weis dictated.

Week 16

Tuesday, September 6, 2004

I updated charts, filed progress reports and made corrections to Study 26 charts. After lunch, I completed and sent history forms and laboratory report forms.

Wednesday, September 7, 2004

I QA'd one Study 26 chart of a patient who had completed the study and faxed a correction. I helped Le Turk, RN, CRC complete a continuing review for the local IRB for Study 24.

Thursday, September 10, 2004

I QAd a chart of a Study 26 patient who had completed the study and sent corrections. I read several articles for my thesis including one I will discuss with my mentor tomorrow on TB in adolescents. After lunch I completed monthly and follow-up evaluation forms. I also helped file a submission for a new study to the IRB.

Friday, September 9, 2004

I worked on the continuing review of Study 26 which is due to the local IRB at the end of the month. I then enrolled one patient into Study 26. Before lunch, the entire research staff met to discuss several issues. Another intern and I presented our analysis of QA and discussed common mistakes found. After lunch I read articles for my thesis.

Week 17

Monday, September 12, 2004

I enrolled two patients and assembled study folders for them. I also completed CRFs for several study patients and QAd several more CRFs before sending them to the CDC.

Tuesday, September 13, 2004

Started a new project today to prepare for Study 26 continuing review to the IRB. We are QAing the Study 26 database with all study charts starting from the beginning of the study to make sure the database was updated appropriately. This way the queries made on the database used to report data to the IRB will be accurate and up to date.

Wednesday, September 14, 2004

Bert Alevaro, our site monitor from Westat, called to suggest that we devise a document for our QA plan. I discussed the plan with Dr. Weis and made a checklist for QAing Study 26 and 27 charts.

Thursday, September 15, 2004

Continued QAing the database for Study 26. Updating this database is not only helping the site conduct accurate continuing reviews, but it will help me with reporting results of Study 26 in my thesis. I completed CRFs in the afternoon.

Friday, September 16, 2004

Today we reorganized the Study 26 charts into active, follow-up, inactive and complete. All charts are now labeled with stickers which correspond to what stage they are in. This will help the coordinators and CSA workers to find charts easier and file them appropriately. I also QAd the computer with 30 Study 26 charts.

Week 18

Monday, September 19, 2004

Enrolled a patient into Study 26. QAd one chart and filed a couple of progress notes. After lunch, I QAd the database with 30 charts, and completed some missing forms to send to the CDC.

Tuesday, September 20, 2004

Updated the computer again today. I QAd 70 charts with the database and fixed corrections.

Wednesday, September 21, 2004

QAd the computer again today with about 55 charts. Then I finished my QA plan for site 20. I also worked on my research thesis today.

Thursday, September 22, 2004

Out of town for a wedding.

Friday, September 23, 2004

Out of town for a wedding.

Week 19

Monday, September 26, 2004

Worked on database audit.

Tuesday, September 27, 2004

Finished database audit. Helped Le complete the continuing review for Study 26.

Wednesday, September 28, 2004

Pulled SAE data for my thesis.

Thursday, September 29, 2004

Pulled AE data for my thesis.

Friday, September 30, 2004

Pulled AE data for my thesis. Left early to write.

Week 20

Monday, October 3, 2004

Met with Dr. Bens to discuss the requirements of the thesis. I worked on my thesis and prepared some data on AEs that I had gathered for Dr. Bayona.

Tuesday, October 4, 2004

Enrolled one patient into Study 26. Attended a meeting with a project manager from Westat to discuss a new epidemiology study that our site will be involved in. Attended an IRB Investigator Training seminar luncheon sponsored by Medtrials and Baylor Research Institute, which discussed Adverse Event Reporting and Analysis. After lunch I helped Dr. Bayona prepare some case studies of "flu-like syndrome" associated with study drugs that she will present at the annual CDC Study 26 meeting at the end of the month.

Wednesday, October 5, 2004

I enrolled two patients into Study 26. Completed case report forms for several follow-up visits. Worked on thesis.

Thursday, October 6, 2004

In the morning I did one correction for Dr. Bayona. I read several articles on TB for my thesis. After lunch I sat in on the clinic with Dr. Weis so that I could learn how to read the chest x-ray.

Friday, October 7, 2004

Completed case report forms. Prepared more cases for Dr. Bayona's presentation. Worked on thesis.

Week 21

Monday, October 10, 2004

Enrolled two patients. DOTd one patient and evaluated the patient. Completed laboratory report forms.

Tuesday, October 11, 2004

Worked with Dr. Bayona on pulling Study 26 cases of drug related flue-like syndrome. Completed case report forms.

Wednesday, October 12, 2004

Enrolled a patient into Study 26. Quality assured a Study 26 chart that had completed the entire study. Completed and faxed two corrections. Used the new QA plan form to QA the chart. Worked on thesis

Thursday, October 13, 2004

Worked on thesis.

Friday, October 14, 2004

Helped Dr. Bayona create PowerPoint slides for her flue-like syndrome presentation at the CDC conference.

Week 22-23

Monday, October 17, 2004

Updated several charts for Dr. Bayona. Completed 6 monthly evaluation forms. Made corrections to the PowerPoint slide and burned it to a disk.

Tuesday, October 18, 2004

Most of the study staff is in Atlanta for the CDC conference. Yesterday, a pregnancy was reported on a Study 26 patient. I created a report for the pregnancy and emailed it to the IRB and the CDC within 24 hours of the event. Dr. Bayona will complete Form 9 and an official report to the IRB when she gets back from the trip.

Wednesday, October 19 -- Friday, October 28, 2004

Devoted this time to pulling data and writing my thesis.

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