TREATMENT OF TUBERCULOSIS FROM PAST TO FUTURE

INTRODUCTION
Humans are locked in a battle with tuberculosis since antiquity. This started with non-pharmacological methods to the discovery of effective medications (streptomycin and para-aminosalicylic acid) in 1944; the development of "triple therapy" (streptomycin, para-aminosalicylic acid and isoniazid) in 1952, assured cure. In the 1970s it was recognized that isoniazid and rifampicin could reduce the duration of treatment from 18 to 9 months, and the observation in the 1980s that adding pyrazinamide to these drugs allowed cures in only 6 months2. To combat noncompliance, intermittent regimens were introduced and second line drugs were advocated for drug resistant tuberculosis3. However, these regimens were not sufficiently short or convenient to follow, they are falling with emergence of extensively drug resistant tuberculosis and have significant problems when used in patients of acquired immune deficiency syndrome4. For these reasons, it is vital that new medications are developed to shorten the duration of therapy, increase the dosing interval of intermittent regimens and replace agents lost to resistance. Other special considerations include identifying optimal therapy for persons with acquired immune deficiency syndrome, particularly noting the problems of drug/drug interactions for those receiving antiretroviral treatment.

DISCUSSION
Eflorts to treat "phthisis" or "consumption" over the millennia have been largely tales of tragedy and frustration. A variety of herbal concoctions, dietary interventions and climatic prescriptions were among the more benign remedies offered. By contrast, bleeding and purging probably amplified and accelerated mortality. However, with the discovery of sulfonamides and penicillin in the 1930s, truly effective antimicrobial therapy became a reality. Selman Waksman's research in New Jersey lead to the identification of streptomycin (SM) in 1944. In the same year PAS (para amino salicylic acid) was synthesized while INH was discovered in 1952. Adding INH to PAS and SM ("triple therapy") resulted in predictable cures for 90–95% of patients. Unfortunately, it required up to 24 months of continuous treatment to achieve this objective5. The replacement of PAS by ethambutol (EMB) in the 1960s had two benefits: EMB was much better tolerated than PAS and it allowed reduction in the duration of treatment to 18 months6. The next major advance in therapy was the introduction of rifampicin (RIF) which further reduced duration of treatment to 8 months. The next step forward was the recognition that the inclusion of pyrazinamide (PZA) allowed a reduction in the duration required to achieve predictable cures.

ISSUES WITH CURRENT THERAPY
Despite progressive reduction, from 24 to 6 months of the duration of therapy required for cure, noncompliance or abandonment of treatment remain the major impediments to effective therapy7. Other issues related to current therapy are drug resistance, side effects of drugs and treatment of patients with HIV co-infection8. The following questions should be asked about new medications.

1. Can they replace medications lost to resistance?
2. Can they improve the performance of conventional regimens versus drug-susceptible disease?
3. Can they be employed in patients with HIV co-infection?
4. Will they solve the mystery of treatment of latent tuberculosis?

Since the year 2000, a number of World organizations have tried to develop a strategy to develop new drugs against Mycobacterium tuberculosis9-12. So far, 9 compounds are in clinical development; 6 in phase III and 3 in phase II trials. The fluoroquinolones (FQNs) are by far the most promising agents. Wild strains of Mycobacterium tuberculosis are predictably susceptible in vitro to the various FQNs, which are currently in preclinical development. A radical new approach to treatment development has been the use of thio-lactomycin derivatives, which have been shown to act on nonreplicating bacilli. Thio-lactomycins have been of somewhat analogues of metronidazole and isocitrate lyase inhibitors. Nitroimidazopryns have been shown to be more active against static M. tuberculosis population than replicating bacilli11,12. Metronidazole itself has limited activity against nonreplicating bacilli, but its analogues may be more active19. Other novel drugs with potential utility against Mycobacterium tuberculosis were recently reviewed by Kremer20. Promising agents included thiolaalcmycins that have activities somewhat analogous, albeit less potent, to INH. Additionally, analogues to pyrazamide or morphazine that may be both more active and noncross-resistant with PZA have been described by a research consortium including Cynamon et al21.

Optimal therapy for tuberculosis in persons with acquired immune deficiency syndrome

The human immunodeficiency virus (HIV) has greatly augmented the TB epidemics in sub-Saharan Africa as well as focal populations of South-East Asia, Latin America, the Indian subcontinent, Russia, and urban, industrialized communities. Most authorities suggest that regimens that are effective among non-HIV-infected TB patients are comparably efficacious in those with acquired immune deficiency syndrome (AIDS)22,23. However, there are problems in this area. Several reports suggest that relapse rates are higher in the presence of AIDS, albeit modestly and so, as with patients with AIDS live longer due to antiretroviral therapy and opportunistic infection prophylaxis, it is plausible that they will survive long enough to allow more relapses. Furthermore, RIF, the mainstay of modern therapy, has such profound pharmacological effects (via induction of the hepatic cytochrome P-450 pathways) that it is not compatible with contemporary antiretroviral regimens24. Rifabutin, which does not have analogous effects on the cytochrome system, has been used as an alternative25. However, it is not free from complicating drug/drug interactions. Rifapentine is another intermediate between RIF and rifabutin in terms of its effect on the cytochrome system26. However, its use in persons with AIDS has been discouraged due to the evolution of rifamycin monoresistance in a small number of patients in a USA Centres for Disease Control trial.

Other problems that loom in this field include possible malabsorption of TB medications and dealing with "the immune reconstitution system" or perhaps most concerning of TB when antiretroviral therapy restores immunologically mediated inflammation27.

CONCLUSION
Considerable work is being directed at finding a vaccine that is more efficient or durable than BCG29. There is also consistent interest in developing an immunomodulating agent, "vaccine" or otherwise, that might help control active disease. This concept is based broadly on the notion that part of the "pathogenic strategy" of TB is the corruption of the human immune response. As tuberculosis disease is initiated and advances in the body, there appears to be a shift from a T-helper cell type 1 (TH1) protective response to a T-helper cell type 2 (TH2) pathway which has several implications. For example, a Vapochelin, a more injurious rapid growing mycobacterium, have been studied in this regard with highly variable results30. Other agents that have been studied or are under consideration include interferon-c31, interferon-c32, miquimod33, interleukin-1234, granulocyte macrophage colony-stimulating factor, levamisole or transfer factor.

Summary
Although the usual case of drug-susceptible TB can be predictably cured in 6 months with a reasonably nontoxic, economical regimen involving as few as 62–78 encounters, novel methodologies must be established if TB is going to be controlled in the decades ahead.
groups available now and in the not too distant future, it is highly likely that the duration of therapy will be able to be reduced to 4 months. To shorten therapy below this level will take either novel agents that are active against the semi-dormant, sporadically multiplying microbes left behind after the initial dramatic killing effects, or an immunomodulatory modulator that substantially enhances the host’s cellular immunity. Unfortunately, despite the massive burden that tuberculosis constitutes, there are no good economic incentives for the pharmaceutical industry to invest in these endeavors. In response, the "Working Alliance for Tuberculosis Drug Development" was formally launched in Cape Town, South Africa in February 2000. It pledged to accelerate the development of new anti-tuberculosis drugs by a system of partnerships, formulation of plans, reassessment of pharmacoeconomics, and advocacy. Sponsored by an array of nongovernmental organizations, private philanthropy and governmental agencies, this "Global Alliance" has embarked upon a vital but formidable task.

Reference