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TUBERCULOSIS/HIV CO-INFECTION

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INTRODUCTION

Tuberculosis (TB) and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) constitute the main burden of infectious disease in resource-limited countries. Estimates by the World Health Orgnisation (WHO) indicate that there are more than nine million new active cases of TB and close to two million deaths per year and 2.6 million new cases of HIV infection and 1.8 million AIDS related deaths occur per year. Myocobacterium tuberculosis-HIV co-infection poses particular diagnostic and therapeutic challenges and exert immense pressure on health care systems in African countries with large populations of co-infected individuals.

In the individual host the two pathogens, M. tuberculosis and HIV potentiate one another, accelerating the deterioration of immunological functions and resulting in premature death if untreated. TB is the largest single cause of death in the setting of AIDS, accounting for about 26% of AIDS-related deaths, 99% of which occur in developing countries.

Both TB and HIV have profound effects on the immune system, as they are capable of disarming the host's immune responses through mechanism that are not fully understood. HIV co-infection is the most powerful known risk factor of latent TB reactivation 20-fold. Likewise, TB has been reported to exacerbate HIV infection. Various lines of evidence indicate that inborn errors of immunity, as well as genetic polymorphisms, have an impact on susceptibility to TB and HIV.

HISTORICAL BACKGROUND

When AIDS emerged in the 1980s TB was a small component of public health in most developing countries, diagnosed by clinicians and treated largely by specialised hospitals. The burden of TB was underestimated, diagnosis was cumbersome and full course of treatment was often unavailable, especially in rural areas. National TB control programmes (NTPs) existed in almost all countries but provided unsystematic management with uncertain results. However, the clinical picture of TB was well understood, and rifampin-based short course regimens had made TB relatively easy to cure, provided the whole course was taken. HIV infection, though made diagnosis even more difficult, complicated management with concomitant infections, increased drug side effects and recurrence and led to five-fold increase in mortality. However, the main impact was caused by the huge increase in cases, putting serious strain on the capacity of NTPs, their workforces, and their budgets. One might have expected almost 30 years after the first reports of HIV-associated tuberculosis (TB), that there would be close co-ordination in policy making on TB/HIV matters internationally and that control programmes would be working closely together at the country level. In fact, neither the TB nor the HIV community has responded adequately to the problems posed by the interaction of TB and HIV infection. Almost all low-income countries had a TB control programme, although some of these programmes are very weak, but HIV treatment programmes are in their infancy, and so is TB/HIV collaboration. This discordance is of real concern for individuals with HIV-associated TB, who can usually access treatment for TB but whose longer term care is uncertain.

Progress is slow because of inadequate political will and insufficient financial, human and institutional resources at the country level, with genuine technical difficulties in co-ordinating a six to eight month treatment regimen provided by one programme and lifelong care provided by another. At both national and global levels, differences in the history and culture of control programmes, exacerbated by territorial protectiveness, have slowed down policy making.

HIV-mediated immunosuppression impairs

granuloma formation, resulting in both ineffective containment of Mycobacterim tuberculosis bacilli and dimished formation of pulmonary cavities. These effects manifest clinically as frequent extrapulmonary disease, a typical chest radiographic findings, greater involvement of the lower lobes of the lung and lower concentrations of bacteria in spatum.

The second problem is limited access to quality microscopy services. The inherent low sensitivity of the test is too often exacerbated by the poor conditions under which it is performed. In overworked, underfunded laboratories, especially in areas where HIV infection is prevalent, the proportion of cases detected by microscopy is often as low as 20-35%. Duplicate or triplicate sputum examinations employed to help overcome this problem – each of which required sputum collection, smear preparation, staining, and meticulous examination – delays results, and a relatively large number of patients do not complete testing or are lost to the health care system despite having tested positive to TB.

Frequent smear-negative disease exacerbates the difficulty of detecting HIV associated TB, leading to additional delays while diagnostic testing or antibiotic treatment trials are being performed. For example, more than a third of patients with smear-negative TB in Malawi needed more than six visits to a health centre before therapy was initiated. Examination of as many as nine sputum smears is recommended before reaching a diagnosis of smear-negative TB in many countries. The failure to rapidly detect TB in immunocompromised populations has important implications both for patient care and disease control. Although the conventional assumption is that smear-negative cases do not contribute significantly to transmission, it is not known whether this holds true in populations in which HIV-associated immunosuppression is common. What is clear is that failure to detect TB early in HIV co-infected individuals is lethal. Up to 20% of all patients with TB who have treatment initiated in sub-Saharan Africa die within a year and two-thirds of these deaths may occur in the first two months, which reflects the advanced state of illness at the time of final diagnosis. Whereas smear-negative TB has conventionally been regarded as a slowly progressive disease with limited mortality, in HIV infected cohorts, patients with smear-negative disease often have poorer treatment outcomes and greater mortality than do their counterparts with smear-positive disease.

The impact that HIVhas on the pathogenesis of tuberculosis is clear. It is one of the most important risk factors associated with an increased risk in latent TB infection (LTBI) progressing to active TB disease. HIV-infected people have an annual risk of 5 to 15% of developing active TB once infected. TB is the most common opportunistic infection in people living with HIV worldwide, it is also the most common cause of death in HIV-positive adults living in developing countries, despite being a preventable and treatable disease.

DIAGNOSIS OF TB IN HIV-INFECTED INDIVIDUALS

Clinical screening algorithms: The WHO recommends TB screening at the time that HIV infection is diagnosed, before the initiation of anti-retroviral therapy and at regular intervals during follow-up.

Currently, there is no internationally accepted evidence-based tool to screen for TB on PLWH.

Radiographic features: The spectrum of radiographic manifestation of pulmonary TB is dependent on the relative level of HIV-related immunodeficiency. During the early phase of HIV when individuals are not immunosuppressed, the radiographic pattern is similar to HIV uninfected individuals with more typical lesions – upper lobe infiltrates with or without cavities. With advancing immunosuppression, extra pulmonary involvement, intra-thoracic / mediastinal lymphadenopathy, lower lobe infiltrate and military TB become more common.

Adding chest X-ray to symptom screening increases the number of TB cases detected but is non-specific and adds to the cost of screening. Chest X-ray can still miss a substantial proportion in individuals with sub-clinical disease, often seen in advanced HIV immunosuppression.

Moreover, chest radiographs may appear normal in 7-14% of patients with HIV / TB. This sub-population of co-infected individuals is particularly likely to benefit from sputum culture or nucleic acid amplification tests for TB diagnosis.

Sputum smear microscopy: The most frequent method of TB detection involves microscopic examination of sputum for acid-fast bacilli (AFB).

Microscopy has the advantage of being inexpensive, relatively rapid to perform, and specific in most settings. However, to be considered smear-positive, a specimen needs to contain approximately 1000 mycobacteria per millilitre. The sensitivity of

sputum microscopy in HIV infection ranges from 43 to 51% and in many resource-limited settings with high rates of co-infection, the sensitivity may be much lower. Methods that improve speed or sensitivity include fluorescence microscopy and alternative specimen processing methods, such as concentration, bleach sedimantation and same-day sputum collection (so called front loading) strategies. Any procedure for digestion or liquefaction followed by centrifugation, prolonged gravity sedimentation, or filtration increase sensitivity by 13-33% over direct microscopy, when culture is used as the reference standard.

The cost of equipment limits the wider use of fluorescence microscopes in resource-limited settings. Alternative technologies using light-emitting diode bulbs allow pluorescence microscopes at a much lower cost; field level evaluation showed promising results and this technology is now being widely scaled up.

Nevertheless, because sputum smear is the primary mode of TB detection in many resource constrained settings, a sizeable number of smear-negative individuals often remains undiagnosed or receive delayed anti-TB therapy. It is also important to note that drug susceptibility cannot be ascertained by smear microscopy, so treatment for drug resistant TB is invariably empirical.

Growth based detection: Culture of Mycobacterium tuberculosis is much more sensitive than smear microscopy and has been recommended to assist of TB in HIV-infected individuals.

Culture also allows subsequent strain characterisation and drug susceptibility tests but is slow. This results in delay in initiation of therapy, with detrimental effects on outcome of HIV / TB co-infected patients. Automated liquid culture systems detect growth of mycobacteria within one to two weeks by bacterial carbon dioxide production or oxygen consumption with radiometric sensors (BACTEC 460 TB).

Molecular techniques: Nucleic acid amplification testing (NAAT) provides a reliable way of increasing the specificity of diagnosis (ruling in disease) but sensitivity is variable, especially in paucibacillary disease.

Commercial kits have the advantage of being well standardised and reproducible. However, concerns about their accuracy, reliability, their high cost, requirement for proper laboratory infrastructure and strict quality control procedures limit their applicability in resource-limited settings.

A recent meta-analysis showed high sensitivity (>95%) and specificity (100%) for line probe assays (LPA) when culture isolates are used. The WHO has endorsed the use of line probe assays which can detect both M. tuberculosis complex as well as isoniazid and rifampicin resistance on smear positive sputum or on early positive growth on culture.

GeneXpert-Rif: Recently, the WHO endorsed the use of GeneXpert-Rif for the rapid diagnosis of TB as well as rifampicin resistance among HIV-infected individuals with clinical suspicion on TB.

GeneXpert is a TB-specific automated, catridge-based nucleic acid amplification assay, having fully integrated and automated sample preparation, amplification and detection using real-time PCR, providing results within 100 minutes. HIV / TB co-infection substantially decreases the sensitivity of microscopy (to 47%) but does not significantly affect Xpert MTB / RIF performance. Xpert MTB / RIF detected rifampicin resistance with 99.1% sensitivity and excluded resistance with 100% specificity. Mean time to detection was <1 day for Xpert MTB / RIF, one day for microscopy, 17 days for liquid culture and >30 days for solid culture. This test seems to have the potential to complement the current reference standard of TB diagnostics and increase its overall sensitivity and speed.

Serological diagnosis of TB Detection of antibodies: Performance of various immune-based tests to detect antibodies to M. tuberculosis antigens has been reviewed extensively.

None of the existing commercial serological tests has adequate sensitivity and specificity to be recommended for diagnostic use. Interestingly, the WHO recently made a negative recommendation to the use of serological tests for TB based on data suggesting that these tests could neither replace sputum microscopy nor be used as an add-on to rule out TB.

Urine LAM assay tends to perform better in HIV-infected compared to HIV uninfected TB patients. The combination of urine liporabinomannan testing and sputum smear microscopy needs further evaluation for use in settings with high HIV burden.

Tuberculin skin test: Tuberculin skin test if positive provides evidence of TB infection. Many HIV infected patients will have a negative skin test despite TB

infection or disease, due to anergy. "Two stage or booster test" is not a substitute to anergy testing; however, it may have some utility in detecting M. tuberculosis infection in anergic HIV-TB co-infected patients.

Tuberculin skin test underestimates the prevalence of latent tuberculosis in endemic coutries. It requires trained health care staff to correctly perform the tests and accurately read the results.

MANAGEMENT OF TB/HIV CO-INFECTION

Co-infection with tuberculosis (TB) and human immunodeficiency virus (HIV) poses a tremendous challenge to TB control, particularly in resource-limited settings. Among patients with active TB, patients with HIV co-infection have greater risk of relapse raising concerns about the optimum duration of TB treatment.

Current recommendations by the American Thoracic Society-Centres for Disease Control and Prevention-Infectious Disease Society of America and the World Health Organisation (WHO) are that the standard six months therapy should be used for active TB in HIV-positive patients, but WHO specifically recommends against using twice-weekly dosing for HIV-seropositive patients.

Anti-retroviral therapy (ART) has been associated with dramatic reduction in the progression to AIDS and death. Studies in a variety of settings have shown that among HIV-infected persons, rates of TB are significantly lower in those who receive ART and progressively decline with longer duration of ART. However, in HIV-infected persons receiving ART, there is scanty data on TB treatment outcomes, and rates of TB remain much higher than in HIV-uninfected persons.

The basic principles of treatment for HIV-associated TB are the same as for HIV uninfected individuals. Certain areas of uncertainty remain, including the regimen duration, dosage and frequency of adminstration of anti-TB drugs, optimal timing of initiation of ART and optimal anti-TB drug combination for patients on second line treatment.

Anti-TB therapy: Currently, standard therapy consists of four drugs in the intensive phase for two months namely isoniazid (H) rifampicin ®, pyrazinamide (Z) and ethambutol (E) followed by H and R in the continuation phase of four months.

Rifampicin plays a key role in the treatment of HIV-associated TB because of its ability to destroy both intracellular and intermittently and slowly growing TB bacilli. Non-rifampicin containing regimens are associated with inferior cure rates and prolong the period of treatment. A meta-analysis on the duration of rifampicin showed that recurrences were two to three times higher if rifampicin use was restricted to two months.

Various studies have shown that there is an increased risk of failures with high probability of acquired rifampicin resistance, especially in ART naive individuals receiving intermittent regimen. This is addition to high recurrence among HIV-infected TB patients led WHO to recommend that daily TB regimens (at least in the initial intensive phase) should be preferred to intermittent regimes among HIV-infected TB patients. Review of the primary evidence indicates very limited, low-quality information on intermittency, mostly from observational studies in the pre-anti-retroviral era. DNA fingerprinting studied in India indicate that most of the recurrences and many of the failures resulted from exogenous re-infection, indicating poor infection control and high transmission, and not poor regimen efficacy. Concurrent ART during TB treatment can turn the tide with high treatment success rates and low fatality, failure and recurrence rates.

THE PROBLEM OF RIFAMPICINS AND DRUG-DRUG INTERACTIONS IN TB AND HIV CO-INFECTED PATIENTS

TB is rapidly fatal, especially in HIV-infected persons. Effective treatment rapidly reduces the number of organisms and renders the person non-infectious. It sterilises lesions to prevent relapse. Multi-drug treatment prevents acquired drug resistance. Single-drug treatment should never be given for active TB. Treatment essentially is curative, and rifampicin, rifabutin or rifapentine which are referred to as rifamycins, are essential in TB treatment.

Treatment of TB in the presence of HIV infection is complicated by drug-drug interactions between rifamycins and PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Both PIs and NNRTIS are metabolised by hepatic CYP3A, especially the CYPA3A4 isoenzyme. Rifamycins are inducers of the CYP3A family of enzymes, which includes the CYP3A4 isoenzyme. Maximal drug level (represented by Cmax) or total drug exposure over time (represented by AUC, area under the

concentration-time curve) of anti-retroviral agents may be reduced when these drugs are co-administered with rifamycins, reducing the efficacy of HAART regimens.

For drug-sensitive TB, several rifamycin-containing anti-TB regimens can be safely administered with effective anti-retroviral therapy. Rifampin and rifabutin are the preferred rifamycins for HIV-infected patients taking PIs or NNRTIs,

RIFAMYCINS AND PIS

While rifampin cannot be used with any of the PIs, rifabutin can be used with regimens containing a single PI-except saquinavir (Invirase) alone – with some dose adjustments. Rifabutin can also be used with the lopinavir/ritonavir (kaletra), fosamprenavir (lexiva/ritonavir, duranavir (Prezista/ritonavir, or tipranavir (Aptivus/ritonavir combinations; Rifabutin should not be used with ritonavir alone because of high rate of adverse effects. For any boosted regimen containing ritonavir, the dose or rifabutin should be reduced.

RIFAMYCINS AND NNRTIS

Some NNRTIs can be used with Rifampin. Rifampin modestly decreases efavirenz (Sustiva, Atripla) exposure. Therefore, it is probably safe to use rifampin concomitantly by prescibing a slightly higher dose of efavirenz, though some investigations report that there appears to be no need to increase the efavirenz dose when administered with rifampin. This regimen is also useful in resource-poor countries where rifabutin is generally not available.

Nevirapine exposure is also reduced by rifampin. Several small observational studies have shown a favourable clinical response for patients receiving rifampin and nevirapine. Co-administration of nevirapine and rifampin may be particularly useful in resource-poor countries for pregnant patients; efavirenz cannot be used in pregnancy and use of PI based regimen is limited because rifabutin is generally not available. If used under these circumstances, close clinical and virologic monitoring should be performed. However, nevirapine is contraindicated in women with CD4+ counts above 250 cells/mm^3 because of an increased risk of severe hepatotoxicity. In such women who are pregnant, a HAART regimen will be difficult to administer during TB treatment in areas where rifabutin is not available. Nevirapine exposure is only slightly decreased by rifabutine exposure. Therefore, nevirapine can be used with rifabutin, both at their usual doses.

While rifabutin can also be used with both efivarenz and nevirapine, another NNRTI, delavirdine should not be used with either rifampin or rifabutin because both of these rifamycins greatly diminish blood concentrations of delavirdine.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

The term paradoxical reaction, coined in the pre-AIDS era, describes the development of new manifestations of TB or worsening of existing signs and symptoms of TB in patients on appropriate anti-TB therapy. It is thought to be due to a reversal of a TB-induced state of energy by effective chemotherapy. IRIS, a term coined in the AIDS era, broadly encompasses a range of inflammatory manifestations temporally related to HAART initiation, resulting either in unmasking a previously occult opportunistic pathogen or in provoking an intensified inflammatory reaction to a concurrent opportunistic pathogen. Presumably, HAART-induced partial immune restoration permits a heightened inflammatory response. This theory is strengthened by the observation that patients with HIV-associated TB who are started on anti-retroviral regimens seem to be a particularly increased risk of developing this syndrome. Thus the timing of HAART initiation in patients with TB is further complicated by the potential for a paradoxical or IRIS reaction.

The frequency of IRIS reaction varies from 11 to 45% and occurs more often in patients with lower CD4+ counts, extra-pulmonary disease, disseminated disease, and with a shorter interval from TB diagnosis to anti-retroviral initiation. Temporally, paradoxical reactions occur within a few weeks of starting anti-retroviral treatment and coincide most closely with viral load decline. The frequency of IRIS was least (13%) in a cohort in which only a minority of patients commenced anti-retroviral therapy prior to the TB diagnosis.

Paradoxical worsening can manifest in a wide variety of sites, including cervical or mediastinal lymphadenopathy, worsening infiltrates on chest radiograph, or enlarging CNS lesions; fever may or may not be present. The course of paradoxical worsening is often unpredictable; it can be brief or prolonged,with multiple recurreces and exacerbations. These reactions typically occur within a few weeks of starting anti-retroviral therapy. The diagnosis of paradoxical reactions remains a

diagnosis of exclusion. Diagnosis relies on negative culture of clinical samples, decrease in HIV viral load, and lack of other aetiologies, such a relapse of infection, poor adherence to treatment, drug adverse effects, worsening TB due to drug resistance, or other infections.

Treatment of paradoxical reactions is not well established. Mild and moderate reactions can be managed by reassuring the patients or by use of nonsteroidal anti-inflammatory agents. Repeated aspirations for decompression of lymph nodes or other extrapulmonary sites have been used to avoid surgical drainage. Some have advocated the use of corticosteroids or discontinuation of anti-retroviral therapy for severe cases – those cases that have lymphadenopathy that may compromise respiration and swallowing, or the development of central nervous system mass lesions. Prednisone at doses ranging from 20 mg to 50 mg daily tapered over as little as two weeks has been used. The use of corticosteroids for these short periods of time does not seem to adversely affect the outcome of the TB treatment. Data on the use of corticosteroids for the treatment of paradoxical reactions in HIV-associated TB are limited; their use should therefore be reserved for severe cases.

SUMMARY

TB/HIV co-infection represents a novel pathogenic scenario at the global level. It constitutes serious diagnostic and therapeutic challenges particularly in poor countries, weighs heavily on already strained health care budgets. It has recently been realised that the epidemology, clinical manifestations, and management of both HIV and M. tuberculosis infections are different and far more complex in co-infected compared to mono-infected patients. However, our knowledge about mechanisms of interaction of the two pathogen still has many gaps that need to be filled in order to develop preventive measures against the two diseases.

Ultimately, the most cost-effective way of combating the two diseases would be vaccination. The present TB vaccine, BGG, does not effectively prevent the most prevalent form of the disease, pulmonary TB in adults. Similarly, no effective preventive HIV vaccine can be discerned on the horizon, although many vaccine candidates are being evaluated in clinical trials. One approach would be to construct a combined TB/HIV vaccine such as a recombinant BGG vaccine as a vehicle fo combinations of mycobacterial and HIV antigens.

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