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Global guidelines for treatment of tuberculosis among persons living with HIV: unresolved issues

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SUMMARY

The Revised National Tuberculosis Control Programme (RNTCP) in India uses a fully intermittent thrice-weekly rifampicin-containing regimen for all tuberculosis (TB) patients, including those who are human immunodeficiency virus (HIV) infected, whereas the World Health Organization (WHO) recommends daily anti-tuberculosis treatment at least during the intensive phase. The WHO recommendation was based on the results of a meta-analysis demonstrating increased risk of recurrence and failure among HIV-infected TB patients receiving intermittent TB treatment compared to a daily regimen. Review of the primary evidence indicates limited, low-quality information on intermittency, mostly from observational studies in the pre-antiretroviral treatment (ART) era. Molecular epidemiology in India indicates that most of the recurrences and many of the failures result from exogenous re-infection, suggesting poor infection control and high transmission rather than poor regimen efficacy. Subsequently published studies have shown acceptable treatment outcomes among HIV-infected TB patients receiving intermittent anti-tuberculosis regimens with concomitant ART. Treatment outcomes among HIV-infected TB patients treated under programmatic conditions show low failure rates but high case fatality; death has been associated with lack of ART. The highest priority is therefore to reduce mortality by linking all HIV-infected TB patients to ART. While urgently seeking to reduce death rates among HIV-infected TB patients, given the poor evidence for change and operational advantages of an intermittent regimen, the RNTCP intends to collect the necessary evidence to inform national policy decisions through randomised clinical trials.

KEY WORDS: HIV; TB; India; intermittent regimen; ART

THE REVISED National Tuberculosis Control Programme (RNTCP) in India has been using a fully intermittent thrice-weekly regimen throughout the treatment period, with a minimum of 6 months of rifampicin (RMP; $2H_3R_3Z_3E_3/4H_3R_3$ for new tuberculosis [TB] patients and $2H_3R_3Z_3E_3S_3/1H_3R_3Z_3E_3/5H_3R_3E_3$ for previously treated TB patients).* The regimen and duration of treatment are the same for human immunodeficiency virus (HIV) positive as well as HIV-negative TB patients.[1] In contrast, the World Health Organization (WHO), in its latest revision of guidelines for the treatment of TB, has recommended that 'TB patients with known HIV-positive status and all TB patients living in HIV-prevalent settings should receive daily anti-tuberculosis treatment at least during the intensive phase'.[2] These recommendations were made by an expert group based on the results of a meta-analysis commissioned by the WHO, which showed that there was an increased risk of recurrence and failures among HIV-infected TB patients receiving intermittent treatment as compared to a daily regimen.[3] It was also observed from a study conducted in India that there was a high rate of acquired RMP resistance among antiretroviral treatment (ART) naïve HIV-infected patients failing anti-tuberculosis treatment.[4] These findings are worrying, and demand that the advantages and disadvantages of a regimen change in the RNTCP be considered.

In this article, we review the primary evidence

*H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin. Numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the number of times the drug is taken each week.

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leading to the WHO recommendation, discuss its applicability from the perspective of a large public health programme and detail the RNTCP's response.

A CLOSER LOOK AT THE META-ANALYSIS

There are several concerns regarding the quality of evidence from the meta-analysis.[3] First, the studies included in the meta-analysis were mostly observational cohort studies from different settings and varying patient characteristics, inherently subject to selection bias. All pooled results must therefore be viewed with caution. Randomised controlled trials (RCTs), which have internal head-to-head comparisons, are considered to be the best in the hierarchy of evidence.[5] No completed RCTs have compared treatment outcomes among patients treated with intermittent or daily regimens containing at least 6 months of RMP. Second, the data on intermittency included in the meta-analysis were limited. Only five cohorts used intermittent regimens, enrolling a cumulative total of 211 patients; of these, two cohorts used RMP only in the intensive phase and another two cohorts used a twice-weekly regimen in the continuation phase. This differs from the RNTCP, which uses a thrice-weekly intermittent regimen with RMP throughout the treatment period of 6–8 months. Third, most of the studies included in the meta-analysis were from the pre-ART era, which is an important difference compared to the current situation in India, where ART is available nationwide. Fourth, the adjusted incidence risk ratios of relapse (4.8, 95% confidence interval [CI] 1.8–12.8) and failure (4.0, 95%CI 1.5–10.4) had wide CIs, indicating huge uncertainties arising from small sample sizes, with limited generalisability. To their credit, the authors of the meta-analysis have acknowledged all these limitations in their article and conclude that 'The most important and striking finding of this review is the paucity of well-designed and adequately powered randomised trials of HIV-TB co-infection treatment. . . . Very basic treatment questions remain unresolved. These questions include optimal dosing, schedule, and duration of rifampicin'.[3] The authors further state that 'Though this review raises concerns regarding the use of intermittent regimens in co-infected patients, the results need to be interpreted with caution, and in view of the low quality of the available evidence, need confirmation through well designed RCTs'.[3] In view of the above described limitations, we consider the evidence about intermittency to be of poor quality.

ENDOGENOUS REACTIVATION OR EXOGENOUS RE-INFECTION?

In high TB incidence settings, re-infection can contribute significantly to recurrent TB disease in HIV-infected persons.[6,7] The distinction is important; previous studies from South Africa have shown that most recurrent episodes of TB among HIV-infected individuals are attributable to re-infection.[8,9] A study from India using three different genotyping techniques confirmed that up to 88% of TB recurrences in HIV-infected patients were due to re-infection, in contrast to 9% in HIV-negative patients.[10] Patients were all treated with similar anti-tuberculosis regimens, and HIV-infected patients did not have access to ART. This suggests that many factors, such as the presence of severe immunodeficiency, poor infection control practices and high background prevalence of TB contribute to continuing transmission of infection, and not just poor efficacy of the treatment regimen used. Another limitation of the meta-analysis, again acknowledged by the authors, was that it could not distinguish between true relapse and re-infection due to lack of genotyping information.[3] In the context of broad evidence identifying re-infection as the attributable cause of most cases of recurrent TB in HIV-infected persons, further information from India on the relative contribution of 'reactivation' and 're-infection' to TB recurrence is essential before drawing conclusions about the efficacy of the chemotherapy regimen.

CONCERNS REGARDING HIGH FAILURE RATES AND ACQUIRED RMP RESISTANCE

Most of the studies on acquired RMP resistance with the use of intermittent RMP-containing treatment in HIV-infected persons were from the pre-ART era, and did not use standardised anti-tuberculosis treatment.[11–14] A study from India found a high risk of treatment failure with acquired RMP resistance in the context of fully intermittent thrice-weekly anti-tuberculosis treatment; this study, however, should be interpreted with caution.[4] First, none of the HIV-infected TB patients enrolled in the study received ART during anti-tuberculosis treatment. Second, genotyping results among failure cases found that many of them were due to a different strain, indicating likely exogenous re-infection.[4] This indicates that even failure during treatment can be a result of exogenous re-infection in high TB incidence settings, and reiterates the essential need to genotype initial and recurrent TB isolates from HIV-infected TB patients before drawing inferences about the efficacy of the anti-tuberculosis regimen.

TREATMENT OUTCOMES IN THE ART ERA

ART has a potent impact on preventing recurrent TB. A study from Brazil showed that ART can halve the risk of recurrent TB among HIV-infected individuals.[15] Results of the recent RCT conducted by the Tuberculosis Research Centre (TRC), Chennai, India, indicates that with ART, the treatment success rates among HIV-infected TB patients treated with

Table Reported treatment outcomes among HIV-infected TB patients registered and treated in the RNTCP, October 2008 to September 2009

State*	TB-HIV cases registered *n*	Treatment success %	Died %	Failure %	Default %	Transferred out %
Andhra Pradesh	9070	76	15	2	5	2
Goa	113	79	14	3	4	1
Karnataka	7893	72	16	1	8	2
Maharashtra	9104	75	14	1	7	3
Manipur	168	77	11	1	10	1
Mizoram	115	77	11	1	6	5
Nagaland	119	70	8	2	10	11
Pondicherry	37	84	8	3	3	3
Tamil Nadu	4513	81	13	1	5	2
Total	31 132	75	15	1	6	2

*Data are from the nine states that offered opt-out HIV testing for all TB patients during this period.
HIV = human immunodeficiency virus; TB = tuberculosis; RNTCP = Revised National TB Control Programme.

intermittent anti-tuberculosis treatment were very high (up to 93% in the efavirenz-receiving arm), with very low rates of recurrence, failure and acquired RMP resistance.[16] Furthermore, an examination of treatment outcomes reported by the RNTCP indicates low failure rates (based on sputum smear examination at the end of treatment) among HIV-infected TB patients; unfortunately, recurrences are not captured by the programme in routine surveillance data.[17] Among the cohort of more than 30 000 HIV-infected TB patients registered from October 2008 to September 2009 from nine states in India, treatment failure rates among initially smear-positive pulmonary TB cases have been reported to be 1–2%, which are very similar to treatment failure rates reported among HIV-negative TB patients (Table). While sputum smear microscopy has limitations in the ascertainment of treatment outcomes, the absence of a difference between the HIV-infected and non-HIV-infected groups in such a large cohort is somewhat reassuring.

On the contrary, the high case fatality (15–17%) among HIV-infected TB patients has been of major concern; although similarly high TB case fatality rates have been reported in HIV-infected TB cases worldwide, this case fatality remains unacceptably high.[18] The highest priority for the RNTCP in TB-HIV care is therefore reducing deaths.

REDUCING DEATHS AMONG HIV-INFECTED TB PATIENTS AND IMPROVING TB-HIV PROGRAMME COLLABORATION

There may be several reasons for the high mortality among HIV-infected TB patients: these include undiagnosed or late diagnosis of HIV, delayed or missed TB diagnosis among persons living with HIV (PLHIV), provision of inadequate chemotherapy to drug-resistant TB cases in the context of unavailability of decentralised culture and drug susceptibility testing facilities, late presentation by TB-HIV patients (indicated by low CD4 counts at the time of diagnosis[19]), and operational issues such as long distances to travel for patients and lack of finances,[20] resulting in suboptimal linkages to centralised ART services. There is no evidence to suggest that case fatality among HIV-infected TB patients can be reduced by changing the schedule of TB drug administration from intermittent to daily.[3]

Available evidence suggests that reductions in mortality may be most effectively driven by efficient, early and improved HIV diagnosis, improved diagnosis of TB among PLHIV, and prompt initiation of ART and TB treatment among HIV-infected TB patients. Results from the SAPIT (Starting ART at Three Points in Tuberculosis),[21] CAMELIA (Cambodian Early versus Late Introduction of Antiretroviral Drugs)[22] and STRIDE[23] trials have all demonstrated the mortality benefit of early compared to deferred initiation of ART during anti-tuberculosis treatment, especially in the subgroup of patients with advanced immunodeficiency. The National AIDS Control Programme's (NACP's) adoption of recent WHO recommendations to treat all HIV-infected TB patients with ART, irrespective of CD4 count, and other measures being put in place to enhance access of HIV-infected TB patients to ART, should help enhance survival.

Programme implementation needs to be strengthened to ensure that all TB patients are offered testing for HIV and, if found to be infected, are linked to an ART centre. HIV testing for TB patients has expanded rapidly in India, with about 65% of TB patients registered in 2010 being tested for HIV, but linkage to ART occurred in less than 50% of co-infected individuals, offering substantial room for improvement.[17] The RNTCP and the NACP have thus jointly planned the following interventions in their next strategic plans (2012–2017):

1 Decentralisation of HIV testing facilities and co-location in all TB microscopy centres to ensure universal coverage of HIV testing among TB patients.
2 Field testing and deployment of improved TB diagnostic tools, such as high-sensitivity cartridge-based nucleic acid amplification tests, for more

effective diagnosis of TB and drug-resistant TB among PLHIV.

3 Early initiation of ART for all PLHIV with CD4 counts of <350 cells/mm^3, and for all HIV-infected TB patients, irrespective of CD4 count. Early initiation of ART is expected to improve immune competency and prevent the development of TB.
4 Providing travel support to all TB-HIV patients to reach ART centres, and supporting patients by creating social welfare schemes to offset patient costs associated with care. Systematic engagement with community networks has also been planned.
5 More than half of PLHIV globally and in India do not know their HIV status and are diagnosed late.[24] Research into the feasibility of 'PITC (provider-initiated HIV testing and counselling) among TB suspects' as a method of achieving early and improved diagnosis of HIV has been planned. Initial results are promising,[25] and broader surveillance is planned to drive policy decisions. Again, earlier HIV diagnosis can broaden opportunities for HIV care and treatment, including TB prevention.

OTHER CONSIDERATIONS IN REGIMEN CHOICE

Before a regimen change (i.e., switch to daily dosing) is considered in India, in addition to regimen efficacy, other operational, logistic and cost considerations need to be taken into account. Intermittent regimens offer a number of advantages. First, intermittent regimens are amenable to direct observation of treatment (DOT) provision under programmatic conditions, which can improve overall adherence.[26] Second, the incidence of adverse drug reactions is reportedly lower with intermittent regimens as compared to daily regimens,[26–29] at least among the general TB patient population. If that general finding is also true for HIV-infected TB patients, this may be particularly important, as the incidence of adverse events (particularly hepatotoxicity, gastro-intestinal side effects and peripheral neuropathy) during simultaneous anti-tuberculosis treatment and ART is relatively high, and adverse events may lead to treatment interruptions for both diseases.[30] This is also important in view of the increasing priority for decentralised treatment provision under the RNTCP, mostly by community treatment providers who are acceptable and accessible to the patient but have limited capacity to manage adverse events. Many clinicians also believe that the incidence of immune reconstitution inflammatory syndrome (IRIS) is less with an intermittent regimen as compared to the daily treatment regimen; however, this information is anecdotal. A clinical trial underway at the TRC is comparing the efficacy (reduction in failure and acquired RMP resistance) and safety of daily vs. fully or partially intermittent anti-tuberculosis treatment among HIV-infected TB patients receiving ART; this study is expected to provide definitive evidence regarding the safety and equivalence of the fully intermittent or partially intermittent regimens.

IN SEARCH OF A REASON TO CHANGE

When considering a regimen change for HIV-infected TB patients, one has to consider that, overall, only about 5% of TB patients in India are HIV-infected.[31] The HIV epidemic in India is concentrated, with an estimated HIV prevalence of 0.31% among the general adult population, and huge heterogeneity across the states and districts.[32] Estimates from 2009 indicate that there were approximately 2.4 million PLHIV in India, with the incidence of HIV showing a declining trend.[32] Another challenge is the fact that HIV prevalence among TB cases is also geographically heterogeneous, with some districts reporting rates in excess of 20% while others are below 2%, adding to the complexity of changing policy at the national level.[17,33] Another meta-analysis compiling arms from RCTs assessed the effect of dosing frequency on treatment outcomes in HIV-negative patient populations.[34] This meta-analysis found no meaningful or significant difference in treatment efficacy in all groups, except for those patients with initial isoniazid (INH) resistance. In these patients, the risk of poor treatment outcomes was substantially higher than in patients without INH resistance in both daily and intermittent short-course chemotherapy arms.[35] While intermittent dosing performed worse in this subgroup, *all* dosing frequencies of short-course chemotherapy yielded unsatisfactory clinical performance. With an estimated 15–20% of patients infected with INH-resistant bacilli, the challenge of detecting and managing INH-resistant TB is considerable, and very little evidence is available to guide treatment options. RCTs are urgently required to develop better therapeutic solutions for a patient group that will be detected with much greater frequency, with the scale-up of services to detect and treat multidrug-resistant TB nationwide.

The RNTCP manages a procurement and supply chain system covering the nation's population and delivering patient-wise drug boxes and other pharmaceutical products to many tens of thousands of service delivery locations for treatment by hundreds of thousands of DOT providers. This supply chain has been very successful, and no district-level anti-tuberculosis drug stock-out of first-line anti-tuberculosis drugs has been reported in over 10 years of programme implementation. Doubling the complexity of this supply chain to provide separate treatment for 1 in 20 patients is not trivial, but could certainly be justified if there were a clear, meaningful advantage in patient-related outcomes to be realised.

NATIONAL EXPERTS UNCONVINCED OF THE EVIDENCE FOR CHANGE

In a national consultation held at the National AIDS Research Institute (NARI), Pune, in January 2011, a group of national HIV and TB experts, researchers, civil society representatives and programme representatives considered the primary evidence and deliberated extensively.[36] The consensus was that the evidence for change was inadequate; hence, the RNTCP should continue using the current regimen and further prioritise early linkage of HIV-infected TB patients to ART. The consultation also recommended that the process of collecting direct evidence from RCTs to inform the question of dosing frequency in HIV-infected TB patients be expedited.

NEXT STEPS

To answer this real and legitimate concern, an RCT powered to assess the effect of dosing frequency on failure and acquired RMP resistance rates is underway at the National Institute for Research in Tuberculosis, Chennai. The study has three arms: 1) a daily intensive phase and a thrice-weekly intermittent continuation phase; 2) a daily regimen throughout; and 3) a thrice-weekly intermittent regimen throughout. Another multisite RCT has been approved by the RNTCP National Standing Committee on operational research to add to the evidence. Large-scale operational research is underway to examine treatment outcomes among HIV-infected TB patients under programmatic conditions, disaggregated by ART, cotrimoxazole preventive therapy status and follow-up, to examine relapse/death rates after 12 months of anti-tuberculosis treatment completion.

CONCLUSION

Although the overall findings of the meta-analysis are worrying, the evidence is too poor to warrant a national change of policy. The RNTCP therefore intends to collect more evidence before making a policy decision.

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RÉSUMÉ

Le Programme National Révisé de Lutte contre la TB (RNTCP) en Inde utilise un régime totalement intermittent trois fois par semaine comportant la rifampicine pour tous les patients de la tuberculose (TB), y compris ceux infectés par le virus de l'immunodéficience humaine (VIH). Pourtant l'Organisation Mondiale de la Santé (OMS) recommande un traitement quotidien de la TB, au moins pendant la phase intensive. La recommandation de l'OMS reposait sur le résultat d'une méta-analyse démontrant un risque accru de récidives et d'échecs chez les patients TB infectés par le VIH et soumis à un traitement intermittent de la TB, par comparaison avec un régime quotidien. La révision des données primaires suggère que l'information sur l'intermittence est limitée et de piètre qualité et provient principalement d'études observationnelles de la période antérieure au traitement antirétroviral (ART). L'épidémiologie moléculaire en Inde indique que la plupart des récidives et un grand nombre des échecs résultent d'une réinfection exogène, ce qui suggère un médiocre contrôle de l'infection et un taux élevé de transmission plutôt qu'une faible efficacité du régime. Les études publiées ultérieurement ont montré des résultats acceptables du traitement de la TB chez les patients TB infectés par le VIH bénéficiant de régimes antituberculeux intermittents concomitants à l'ART. Les résultats du traitement chez les patients TB infectés par le VIH et traités dans les conditions du programme montrent de faibles taux d'échec, mais une létalité élevée ; le décès a été associé à l'absence d'ART. Dès lors, la priorité principale est de réduire la mortalité en veillant à ce que tous les patients TB infectés par le VIH bénéficient de l'ART. Alors qu'il cherche à réduire d'urgence les taux de décès chez les patients TB infectés par le VIH, le RNTCP, vu la médiocrité des évidences en faveur d'une modification des avantages opérationnels d'un régime intermittent, a l'intention de collecter les preuves nécessaires pour donner aux décisions politiques nationales les informations provenant d'essais cliniques randomisés.

RESUMEN

En el Programa Nacional Revisado de Control de la Tuberculosis (RNTCP) de la India se administra, del principio al fin del tratamiento, una pauta intermitente tres veces por semana que comporta rifampicina a todos los casos de tuberculosis (TB), incluidos los pacientes con infección por el virus de la inmunodeficiencia humana (VIH). No obstante, la Organización Mundial de la Salud (OMS) recomienda una pauta de tratamiento diario como mínimo durante la fase intensiva. La directiva de la OMS se basó en los resultados de un metanálisis, según el cual los pacientes con TB y coinfección por el VIH presentaban un mayor riesgo de recaída y fracaso cuando recibían un tratamiento antituberculoso intermitente, que cuando que seguían un tratamiento diario. Un análisis de los datos primarios de este estudio puso en evidencia una información escasa y de calidad deficiente sobre la intermitencia, sobre todo en los estudios de observación realizados durante la época previa a la administración del tratamiento antirretrovírico (ART). Los datos de epidemiología molecular de la India indican que la mayoría de las recaídas y muchos de los fracasos terapéuticos son consecuencia de reinfección exógena, lo cual refleja más un control deficiente de las infecciones y una alta tasa de transmisión que una ineficacia de la pauta terapéutica. En algunos estudios publicados posteriormente se han demostrado desenlaces terapéuticos aceptables en pacientes coinfectados por el VIH que reciben pautas antituberculosas intermitentes y ART concomitante. En los desenlaces terapéuticos de pacientes tuberculosos infectados por el VIH que reciben tratamiento en las condiciones del programa, se observan bajas tasas de fracaso, pero un alto índice de letalidad; la mortalidad se ha asociado con la falta de ART. En consecuencia, la mayor prioridad consiste en disminuir la mortalidad, mediante la inscripción al ART de todos los pacientes tuberculosos infectados por el VIH. Al mismo tiempo que se busca con urgencia disminuir las tasas de mortalidad en estos pacientes y dadas las insuficientes pruebas en favor de un cambio y las limitadas ventajas operativas de una pauta intermitente, el RNTCP de la India se propone llevar a cabo ensayos clínicos aleatorizados con el objeto de recoger los datos necesarios que documenten la toma de decisiones sobre políticas nacionales.