pISSN: 0976 3325 eISSN: 2229 6816

REVIEW ARTICLE

EVALUATION OF ISONIAZID PREVENTIVE THERAPY POLICY

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Keywords: Tuberculosis, Isoniazide Preventive Therapy, National Progrrame, HIV / AIDS

BACKGROUND INFORMATION

HIV is the strongest risk factor for developing tuberculosis (TB) disease in those with latent or new Mycobacterium tuberculosis infection [1]. The risk of developing TB is 21- 34 times greater in people living with HIV than among those who do not have HIV infection [1]. TB is responsible for more than a quarter of deaths among people living with HIV [2]. At the end of 2009, 33.3 million people worldwide were living with the human immunodeficiency virus (HIV), and 95% of them resided in low- or middle-income countries [3]. The estimated number of children living with HIV increased to 2.5 million in 2009. The proportion of women living with HIV has remained stable, at slightly less than 52% of the global total [3]. Approximately 5 million people were receiving antiretroviral therapy (ART), but an estimated 10 million were still in need of ART [3]. Although global initiatives such as the United States President's Emergency Plan for AIDS Relief [4] and the Global Fund to Fight AIDS, Tuberculosis and Malaria [5] have focused on scaling up ART, millions of people living with HIV remain eligible for and could benefit from prophylaxis against TB thorough Isoniazid (INH) preventive therapy (IPT).

National HIV programmes are usually responsible for initiating intensified case-finding for TB among people living with HIV as well as for providing IPT to those without active TB. However, in 2009, of the estimated 33 million people living with HIV, only 1.7 million (5%) were screened for TB, and about 85,000 (0.2%) were offered IPT, a treatment that can greatly reduce a person's risk of developing TB disease [3]. The goal of this paper is to evaluate exiting Isoniazid preventive therapy (IPT) policy, identify challenges for low IPT coverage and suggest possible recommendations to improve the same.

ISONIAZID PREVENTIVE THERAPY (IPT) POLICY

TB is the most frequent life-threatening opportunistic disease among people living with HIV (PLHIV) and remains a leading cause of mortality, even among persons receiving ART [6-12]. Clinical trials have shown that IPT dramatically reduces the incidence of TB among people living with HIV[6-12]. A 2004 Cochrane Review found that IPT reduced the risk of TB by 33% overall and by 64% when targeted to people living with HIV who had a positive tuberculin skin test [13]. A retrospective study also showed that IPT significantly reduced the incidence of TB even among people living with HIV and receiving ART [14]. In 1998, World Health Organization (WHO) and UNAIDS (Joint United Nations Programme on HIV / AIDS) issued a statement that recognized the effectiveness of IPT among people living with HIV and recommended its use as part of an essential care package for these patients [15]. As per this statement, the following prerequisites were identified, which should be in place before an IPT service is considered [15]:

- Adequate capacity for HIV counseling
- Sufficient trained health care staff
- Linkage between HIV care and TB control services
- TB treatment services that have a high probability of curing cases of TB identified through the IPT service

In settings meeting these standards, WHO and UNAIDS recommend to governments that [15]: -

1) IPT should be part of a package of care for people living with HIV / AIDS.
2) IPT should only be used in settings where it is possible to exclude active tuberculosis cases and to ensure appropriate monitoring and follow up.
3) Information about tuberculosis including IPT should be made available to people with HIV.
4) IPT should be provided from within settings that include established voluntary counseling and testing (VCT) services for HIV.
5) The priority for TB control programmes continues to be the detection and cure of infectious tuberculosis cases.
6) The procurement and supply of tuberculosis drugs must be regulated by national authorities, in order to prevent the development of drug resistance.

The WHO recommended regimen for TB preventive therapy in adolescents and adults living with HIV is Isoniazid [isonicotinic acid hydrazide (INH)] 300 mg daily for at least 6 months [16]. These recommendations were reinforced in a statement released by the TB / HIV working group of the Stop TB Partnership in October 2007 [16]. WHO guidelines on essential prevention and care interventions for people living with HIV also recommend IPT for these individuals [17]. Despite strong recommendations by WHO and UNAIDS since 1998, less than 1% of HIV positives received IPT in 2009 as part of National HIV programme [3]. Recent WHO guidelines on TB screening and IPT, among people living with HIV, recommend screening using four symptoms (current cough, fever, weight loss and night sweats) and providing IPT if these symptoms are absent [18]. This symptom-based screening algorithm has been found to have a negative predictive value of 97.7% (95%confidence interval, 97.4–98.0) in settings where the prevalence of TB among people living with HIV is 5% [19].

The IPT policy recommendation has not been implemented by many countries as part of their National HIV programme. There are many practical issues hindering implementation of this policy, including capacity of National HIV programmes and ability to rule out active tuberculosis among HIV infected population for most resource constrain countries.

ISSUES/CHALLENGES WITH IPT POLICY

There is gap between number of countries support IPT policy and number of countries actually implementing IPT policy. The number of countries supporting the IPT policy has increased from 8 to 102 between 2002 and 2009, however only 41 countries has reporting on actual implementation of IPT policy in 2010 [20]. This is a clear illustration of the gap between the support / existence of the IPT policy and the actual implementation.

Currently there is no internationally accepted evidence-based tool to screen for TB in people living with HIV [21]. Many studies have shown the difference between symptoms and sign of TB among people with and without HIV; for example, many people living with HIV who have culture-confirmed TB do not report having a prolonged cough, which is one of the standard TB screening questions used by national TB control programs globally [21]. Most resource constrain countries are using sputum smear microscopy or chest radiography to diagnose TB among PLHIV, most PLHIV have either sputum smear negative pulmonary TB or extra pulmonary TB which are difficult to diagnosed using this technologies [22]. Therefore, it is difficult to rule out active TB among HIV positive in resource limited settings. Thus, there is strong concern among programme managers to start IPT without ruling out TB, which can increases chances of drug resistant TB. The emergence of drug resistant TB (MDR and XDR) in countries with a high HIV prevalence poses an additional public health threat for entire community. However, studies demonstrated that there is no significant increased risk of INH monoressistance following IPT[23-24].

Use of Tuberculin Skin Test (TST) to rule out active TB, requires well trained and experienced staff to interpret the results in addition to repeated visits by the patient [25]. Also, HIV-infected persons have a compromised ability to react to the skin test. Due to operational and technical issues, TST is not used in most resource constrain high HIV burden countries [25].

Policy and health worker related issues, like lack of experience, knowledge, and clarity on the benefits of IPT and existing guidelines on IPT among health workers were important barriers for IPT provision rather than patient-related factors [26]. Existing global national policies do not explicitly address the drug management issue for INH, as INH is part of the National TB Control Programme [27]. Anecdotal evidence suggests that this has resulted in no access to the drug for HIV implementers to procure quality

INH to be used as a prophylaxis for PLHIV [28]. Adherence to INH is important for individuals receiving IPT; however there are no studies available that examined the efficacy of adherence at population level [28].

The critical component of TB/HIV collaborative activities is, monitoring and evaluation to provide the means to assess the quality, effectiveness, and coverage of services, however most resource constrained countries have not established a system to monitor IPT as part of collaborative TB/HIV activities [27].

A cross-sectional survey of WHO HIV/AIDS programme officers concluded the main issues/challenges for IPT policy were: (i) inadequate intensified TB case-finding because of the inability to exclude active TB, (ii) logistic difficulties in performing tuberculin skin tests to diagnose latent TB infection, and (iii) concerns regarding inadequate patient adherence potentially leading to isoniazid monoresistance [29]. There can be many reasons for poor implementation of IPT policy globally, however the lack of national consensus and political commitment has resulted in limited scale up IPT in most resource constrain countries [28].

RECOMMENDATIONS for strengthening implementation of IPT Policy

Solutions for effective implementation of IPT policy require different actions at multiple levels. Unequivocal endorsement of IPT globally and a clear direction and bold leadership from the highest political level nationally are crucial for strengthening IPT scale up as integral part of HIV/TB collaborative activities [29]. Development of clearly articulated global policy for IPT based on technical consensus among technical partners and experts (HIV and TB control programmes) across the globe should be followed by development and dissemination of national policy from national to grass root level. IPT policy implementation should be an integral part of a National HIV programme and TB/HIV collaborative activity plan [3]. Countries need to develop detailed and clear operational guidelines for implementation of the same. The national policies with regional and state level time bound targets are necessary to scale-up implementation of IPT policy through mobilization of political commitment and engagement of stakeholders from national HIV and TB control programmes.

Global and national networks of PLHIV should play very important role for IPT policy scale up as part of their advocacy work both nationally and at the grass root level [28]. HIV Positive people networks, International and national NGOs and activists can play major role to mobilize policy makers in rollout of IPT policy as part of National HIV programme [28]. Awareness activities should be carried out among PLHIV to consider IPT as an evidence-based effective intervention, which should empower PLHIV to demand IPT during their encounter with HIV service providers.

The WHO has recently revised the guidelines on IPT that recommends the use of a simplified screening algorithm that relies on the absence of all four clinical symptoms (current cough, night sweats, fever, and weight loss) to identify those PLHIV who have less likelihood of active TB disease and hence are eligible for IPT [18]. As per the revised guidelines, chest radiography is no longer required as a mandatory investigation before starting IPT and TST is not a requirement for initiating IPT for PLHIV [18]. This simplified symptom-based algorithm should be used for all adults living with HIV, including pregnant women, people who are receiving ART, and those who successfully completed TB treatment [18]. Few resource constrain countries (e.g. South Africa and Cambodia) have adopted and implemented the revised WHO guidelines in 2010 [1]. In South Africa, the number of people living with HIV who were provided with IPT increased by more than five-fold in one year, from 23 583 in 2009 to 124 049 in 2010, while in Cambodia, these numbers increased seven-fold in one year, from 66 in 2009 to 491 in 2010 [1]. seng

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