

Implementation of isoniazid preventive therapy for people living with HIV worldwide: barriers and solutions

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Introduction

Tuberculosis (TB) is the most frequent life-threatening opportunistic disease in people living with HIV (PLHIV) in the first 3 months of antiretroviral treatment (ART), in both industrialized and resource-constrained settings [1,2]. ART significantly but not entirely reduces the risk of TB disease [3]. It is also associated with significantly increased mortality both before and during ART [4–6]. Morbidity and mortality from drug-sensitive and drug-resistant TB among PLHIV are unacceptably high [7,8]. For all these reasons regular screening of all PLHIV for active TB disease and provision of either treatment for active disease or preventive therapy, and the provision of earlier ART [9] along with other measures to minimise TB transmission are essential.

The World Health Organization (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 [10–13]. Assessment of the duration of isoniazid preventive therapy (IPT) detected no significant difference in efficacy between 6 and 12 months [14]. Although 9 months of IPT is supported by evidence and

recommended in some guidelines, there are no studies that have directly compared it either with 6 or 12 months of IPT. Two trials from Botswana [15] and South Africa [16] suggested increased benefit with 36 months or longer duration of IPT than with a 6-month regimen, particularly in people who have a positive tuberculin skin test (TST). However, no difference in benefit was observed between a 6-month and 36-month duration IPT in a clinical trial that was conducted in India [17].

In children living with HIV and presenting with or without positive TST, IPT was shown to reduce early mortality by 50% and incidence of TB by 70% in a small, randomized trial where ART was not widely available [18]. However, clinical trials in adults have shown no survival benefit of IPT [19–22], although one cohort study showed a survival advantage [23]. In all studies, isoniazid was generally safe and well tolerated [20].

In 1993, the WHO first issued a policy statement that recognized the efficacy of TB preventive therapy and recommended targeting IPT in PLHIV [10,24,25]. That was also the year when TB was declared a global emergency [26]. It was also packaged as one of the 12 collaborative TB/HIV activities recommended by WHO

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in 2004 [10] and repackaged as part of the Three 'I's for HIV/TB (isoniazid preventive treatment, infection control for TB, and intensified case finding) in 2008 [27]. It also revised its policy on IPT in 2010 reiterating the importance of IPT as a core function of services provided to PLHIV and as a primary responsibility of National AIDS Programs.

The purpose of this article is to discuss the global progress in the implementation of IPT as a public health intervention between 2002 and 2009, and to review critical health system barriers for its nationwide implementation. It offers simplified strategies and critical steps that are essential to scale up its implementation in high HIV prevalence countries.

Methods

We used the existing WHO systems of data collection to present the progress of implementation of collaborative HIV/TB activities. The system relies on information provided by countries to WHO through its global TB monitoring and evaluation system [28]. Data on collaborative TB/HIV activities are also collected through the joint data collection system of WHO, United Nations Children's Fund, and Joint United Nations Program on HIV/AIDS (UNAIDS) as part of the system that monitors and reports on progress in the health sector response toward universal access of HIV/AIDS services [29]. Data collection forms of the TB monitoring and evaluation system had been sent only to the top 41 countries with the highest burden of HIV-related TB between 2002 and 2005. Starting in 2006, forms were sent to all WHO Member States and territories. The joint WHO, United Nations Children's Fund, and UNAIDS data collection system, which collects information on several indicators on HIV/AIDS services, included IPT data collection only in 2008. Data are collected from both National TB and AIDS Control Programs. There is a set of standardized HIV/TB indicators harmonized among the agencies that enhance the accuracy and reliability of the data collected [30].

We used a combination of systematic review, document analysis and global expert opinion to present the barriers for scaling up of IPT implementation. We searched PubMed for combinations of the search terms 'isoniazid', 'prophylaxis' or 'prevention' with 'HIV', 'tuberculosis', 'challenges', and 'barriers'. We considered publications in English with no limit on time. We also reviewed reports and presentations of WHO TB/HIV meetings that were conducted in 2003–2009. We used the framework of the six components (pillars) of the health system to present the key health system-related barriers for scaling up the implementation of IPT [31].

Results and discussion

Global implementation of isoniazid preventive therapy

Table 1 illustrates the progress of implementation of IPT between 2002 and 2009, showing 19-fold increase over this period. Almost a quarter of a million PLHIV (242 847) were reported to have received IPT. The 85 000 PLHIV who received IPT in 2009 as reported to WHO represent only 1.3% of the 6.6 million PLHIV who are estimated to know their HIV status (the assumption used is that one out of five PLHIV are aware of their status [29]). Comparatively very few countries were providing IPT from the South East Asia and Western Pacific regions.

Figure 1 shows the proportion of PLHIV among whom active TB was excluded so that IPT could be provided. Very few countries reported the provision of IPT and even those that reported the activity mostly provide it for less than 1% of PLHIV.

Barriers to scaling the implementation of IPT

Barriers to the implementation of IPT are diverse and can occur from global to facility levels. Table 2 summarizes key health system-related barriers for scaling up the implementation of IPT listed by the six components (pillars) of the health system [31].

Leadership and governance-related

The 1998 WHO and UNAIDS policy on IPT recommended the implementation of IPT with mandatory chest radiography to exclude active TB and a targeted approach for individuals with a positive TST result. However, noting TST is not feasible in most settings, the policy recommends IPT in populations with more than 30% prevalence of *Mycobacterium tuberculosis* infection and other target groups such as healthcare workers, household contacts of patients with TB, prisoners and miners [25].

The number of countries that issued supportive policy for IPT implementation has progressively increased from 8 to 102 between 2002 and 2009. However, only 27–50% of those countries with supportive national policies actually reported the provision of IPT for PLHIV per year during the period [32]. This is a clear illustration of the gap between the existence of a policy and the actual implementation of IPT. Although there can be many reasons for this gap, some national policies can impede wider implementation of IPT. Such attitudes most likely emanate from the concerns by program managers and service providers of inadvertent monotherapy with INH for undetected TB that could give rise to the development of INH resistance.

The fear of development of drug-resistant TB is one of the reasons commonly cited among program managers and service providers for limited scaling up [33]. Studies

Table 1. Numbers of individuals who were given isoniazid preventive therapy 2002–2009.

Country/area ^a	2009	2008	2007	2006	2005	2004	2003	2002	Total
Botswana	11 732	12 802	6042	19034	18762	11 738	6195		86 305
South Africa	23 583	7359	5642	2512	1466	234	734	2498	44 028
Russian Federation	10 451	6933	5768						23 152
Namibia	17 737								17 737
Ethiopia	2403	1493	2381	1399	1983				9659
Haiti		7250	974						8224
Ukraine	4980	2763							7743
Peru	1361	2137	1519		1214				6231
Uzbekistan	1056	1046	1098	1314					4514
Nigeria	1853	2099	76			45	12		4085
Mozambique	2429	724	676	109					3938
Dominican Republic		443	848	1033	953				3277
Mexico	676	1490							2166
Vietnam	1500	500							2000
Rwanda							980	980	1960
Kazakhstan	1027	656	206	13					1902
Cuba	1561		297						1858
Guyana	162	132	744	610					1648
Zambia		850						339	1189
Burundi	617		416						1033
Iran (Islamic Republic)	418	443							861
Guatemala	250	20	575						845
Thailand	127	206		444					777
Nicaragua	60		656						716
Brazil					674				674
Panama	196	16	8		400				620
Malawi								569	569
Georgia		301	235						536
Belize			10	26	409				445
Papua New Guinea		47	215	183					445
Venezuela	102	76	109	110					397
Romania	188	188							376
Myanmar	333								333
Cambodia	66	66	77	53			24		286
China, Hong Kong SAR	78	75	63	64					280
Libyan Arab Jamahiriya		144	116						260
Honduras	96	153							249
Zimbabwe		226							226
El Salvador	97		110						207
United Republic of Tanzania	153								153
Tunisia	24	51	19	29					123
Uganda			121						121
Tajikistan		23	75						98
Netherlands		90							90
Bulgaria	9		54						63
Kyrgyzstan	58								58
Oman			5	50					55
Bolivia					50				50
Iraq		45							45
Guinea-Bissau				42					42
Trinidad and Tobago	4	6	17	4					31
British Virgin Islands					27				27
Lebanon	19	5							24
Turkey			15						15
China, Macao SAR	1		9	2					12
Saudi Arabia		12							12
Lithuania				11					11
Armenia		1	1	8					10
Barbados			10						10
Sri Lanka	5	2	1						8
Albania	3	2	1						6
Mauritius			3	2					5
Dominica	2		1						3
Ecuador		3							3
Qatar		2	1						3
Jordan	2								2
Sao Tome and Principe	2								2
Timor-Leste	2								2
Bahamas		2							2
Comoros				2					2

Table 1 (continued)

Country/area ^a	2009	2008	2007	2006	2005	2004	2003	2002	Total
Egypt	1								1
Philippines	1								1
Saint Vincent and the Grenadines	1								1
Anguilla			1						1
Cyprus				1					1
Grenada				1					1
Guam		1							1
Northern Mariana Islands			1						1
Total number of people living with HIV provided with IPT	85 426	50 883	29 196	27 056	25 938	12 017	7945	4386	242 847
Number of countries/areas reporting	44	43	42	25	10	3	5	4	

The data are based on routine reporting from the National AIDS and TB Control Programs of the countries. Although a standardized system is in place to ensure the validation of data collected, it is not always possible to obtain data from some countries consistently over the years because of lack of well established monitoring and evaluation system in some countries. Some countries (e.g., Malawi and Rwanda) stop the provision of isoniazid preventive therapy (IPT) due to a policy change after reporting the activity in earlier years. The timing and cycle of data collection was changed for 2009 in order to reduce the reporting gap into 1 year. Therefore, not all countries that reported the activity in 2008 were able to comply with the deadline. TB, tuberculosis.

^aData collection forms were sent only to the top 41 countries with the highest burden of HIV-related TB between 2002 and 2005 and to all countries and territories ($n = 211$) after 2006.

demonstrated that there is no significant increased risk of INH monoresistance following IPT [34,35].

Service delivery-related

The TST is used to identify skin test positive persons who have latent TB infection and who would benefit from IPT, mainly in low TB incidence and high-income countries [36]. However, aside from its expense and difficulties with logistics, it has several known operational and technical limitations including poor specificity, cross-reactivity with BCG (Bacillus Calmette-Guérin) vaccination and nontuberculosis mycobacteria, and poor reproducibility [37]. Implementation of TST requires well trained staff, and interpretation of the result requires a thorough experience and repeated visits by the patient

[38]. Moreover, HIV-infected persons have a compromised ability to react to the skin test because of cutaneous anergy associated with immunosuppression [39].

Studies reported that the numbers of PLHIV need to be treated with IPT in order to prevent one case of TB ranged from 6 to 70 depending on the incidence of TB at baseline, length of trial follow-up, and individual factors such as skin positivity for TST [14,40,41]. The commonly cited pooled number needed to treat for PLHIV with IPT to prevent one case of TB is 50, which lowers into 20 if the person is TST positive [14]. However, the interpretation of such pooled numbers need caution, as the baseline risk often varies appreciably among trials [42].

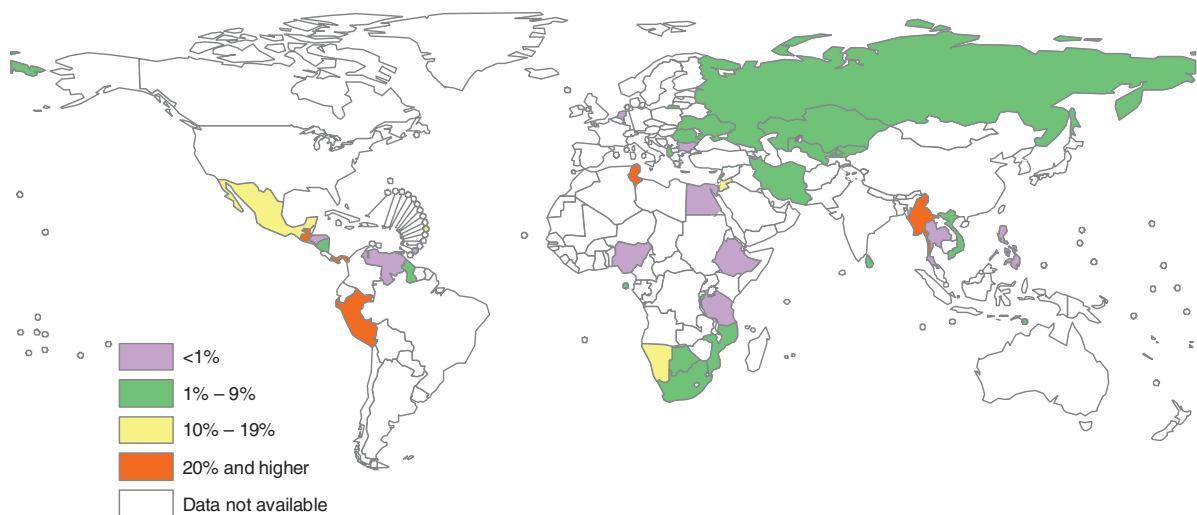


Fig. 1. Map showing percentage of people living with HIV screened for tuberculosis and without tuberculosis who received isoniazid preventive therapy out of all estimated people living with HIV (excluding those who were identified with active tuberculosis) in the country, 2009.

Table 2. Health system barriers for the nationwide implementation of isoniazid preventive therapy.

Leadership and governance-related	Service delivery-related	Supplies and products-related	Health workforce-related	Health information system-related	Health system financing-related
Neglect of TB as a core component in HIV care and treatment services	Lack of simple, effective, and point-of-care TB diagnostics	Unavailability of laboratory services and supplies	Provider behavior toward clients and perception on IPT	Lack of monitoring and evaluation system	Competing priorities for resource allocation
Lack of leadership by AIDS programs and HIV stakeholders	Unavailability of standard TB screening algorithm and operating procedures	Ineffective TB and HIV supply management	Lack of training and supervision capacity	Lack of standardized indicators	Quest for cost-effectiveness
Reluctance and negative perception of program managers	Nondecentralized HIV services	Unavailability of PPD for skin test and cold chain needs	Referral and other communication failures		
Perceived fears of resistance to INH	Difficulties with the administration of tuberculin skin test	Shortage of INH (e.g., INH, 300 mg) and HIV test kits	Lack of knowledge of HIV status of clients		
Weak links and collaboration between TB and AIDS programs	Poor adherence by clients		Fear of toxicity of INH and generating drug resistance		
Exclusive control of INH as anti-TB drug by National TB Control Programs					
Total absence and/or presence of restrictive national policies					

INH, isoniazid; IPT, isoniazid preventive therapy; PPD, purified protein derivative; TB, tuberculosis.

There are no studies that examined the effect of individual adherence to IPT on its efficacy at a population level. However, there are a few studies that examined the effect of adherence on individual outcome and measured adherence in different ways [12,43,44]. Number of clinic visits [43], pill collection [45], pill count [12], and urine test [45] were used to measure adherence for IPT. Adherence rates for IPT vary significantly, and shorter duration of treatment and peer support were identified as factors that improve adherence [11,12,43,44,46]. Adherence is important for individuals to realize the full risk reduction benefit of isoniazid preventive treatment; however, given the low bacillary load should they stop their course of treatment it does not have the same implications as stopping treatment for TB.

Supplies and product-related

Existing global and national policies do not explicitly address the drug management INH for use as prophylaxis apart from stating that National TB Control Programs (NTP) should actively participate in drug logistics and procurement [25]. Being an anti-TB drug, INH is often under strict NTP control in those countries implementing the Stop TB Strategy. 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.

Health workforce-related

In clinical trials and clinical practice, IPT is well tolerated in PLHIV. The most serious adverse reaction is hepatotoxicity, which occurs in a very small proportion of individuals receiving treatment ranging between 0.001 and 0.004% [20,47,48]. The risk of hepatitis increases with age of more than 35 years [48,49]. However, the benefits of IPT outweigh the risk of hepatitis in the presence of HIV infection in people with age of more than 35 years [50]. Similarly, the risk of hepatitis increases with excessive alcohol use [48]. Alcohol use was reported in 11% of PLHIV receiving 6-month IPT in Botswana [51]. Lack of experience, knowledge, and clarity on the benefits of IPT and existing guidelines by health workers were cited as important barriers for IPT provision rather than patient-related factors [52].

Health information system-related

The monitoring and evaluation of collaborative TB/HIV activities, in which the provision of IPT is one critical component is important to provide the means to assess the quality, effectiveness, and coverage of services [30]. Not many resource-constrained countries have an established system to monitor and evaluate the implementation of collaborative TB/HIV activities, including the provision of IPT [53]. Furthermore, reporting requirements from donor agencies that are not harmonized with internationally and nationally agreed indicators and processes place unnecessary burden on programs [30,54].

Health system financing-related

Over the last decade, there has been an increased availability of funds particularly through the President's Emergency Plan for AIDS Relief (PEPFAR) [54] and the Global Fund to AIDS, TB and Malaria (GFATM) [55] for collaborative TB/HIV activities. However, the lack of national consensus and political commitment resulted in limited utilization of these funding opportunities to scale up IPT. There are reports that some countries requested for reprogramming of approved funds for scale up of IPT from the GFATM because of lack of national policy and consensus (unpublished communication, GFATM).

There are a number of studies that explored the cost-effectiveness of IPT implementation. The provision of IPT for PLHIV resulted in monetary savings in medical care and social costs [56]. A study in South Africa concluded that IPT provision is cost saving after it was found that US\$ 92–183 was needed for completing a 6-month course [57]. None of the studies took place in a population that is also on ART.

Solutions to promote nationwide scale-up of isoniazid preventive therapy implementation

Create a conducive national policy and program environment

Implementation of IPT should be a priority for National AIDS control programs, not only in high HIV prevalent settings but also countries with concentrated or low-level HIV epidemics. Policies with national time bound targets are necessary to scale-up of implementation of IPT. This facilitates implementation and also helps to mobilize political commitment and engagement from TB and HIV stakeholders. Unequivocal endorsement of IPT, a clear direction, and bold leadership from the highest political level in government coordinating the country's AIDS response (e.g., National AIDS Commission) and the Ministry of Health are crucial to promote nationwide scale-up of IPT along with other collaborative TB/HIV activities.

Similarly, the development of a conducive operational environment needs to be prioritized. All national and local HIV training modules and training efforts need to include IPT as an essential element of providing HIV care and treatment and also to address misconceptions among service providers. Clear, simple and nonrestrictive operational guidelines should be developed.

Adopt the simplified symptom-based algorithm for tuberculosis screening and isoniazid preventive therapy provision

WHO has revised its guidelines on IPT and 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 [58]. Chest radiography is no longer required as a mandatory investigation before starting IPT and TST is not a requirement for initiating IPT for PLHIV [58]. 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 [58]. It is worth noting that protective benefits of concomitant use of IPT with ART were demonstrated in two observational studies from Brazil [59] and South Africa [60], and a subanalysis of an unpublished randomized clinical trial data from Botswana [15].

Client monitoring and education

Client monitoring and education can reduce the risk of serious INH-related toxicity [49]. Clients should be warned about symptoms of INH toxicity (abdominal pain, nausea, and jaundice) and told to stop taking INH and return for evaluation if these occurs. They should also be warned about alcohol consumption while on IPT. Monthly monitoring for symptoms is very effective, but may not be practical in all settings. PLHIV and receiving IPT should have regular clinical follow-up based on the national, local, and clinical context. This includes regular screening using the symptom-based algorithm at every contact with healthcare providers. Programs implementing IPT are encouraged to introduce national TB drug resistance surveillance systems in accordance with internationally agreed guidelines [61].

Adherence to therapy is an important issue, and interventions to promote adherence may be very useful. Various incentives and enablers have been shown to improve adherence in diverse populations of people receiving IPT. Client education [48] is an effective strategy for increasing adherence. The use of a 300 mg INH formulation, and a fixed-dose combination of INH and co-trimoxazole, which is being explored might improve adherence as well.

Ensure effective isoniazid access and supply system

In countries where there are structural, regulatory, and political problems that impede INH access for HIV stakeholders, National TB and AIDS Control Programs should ensure that adequate supplies of INH are readily available for HIV care programs. Isoniazid (pediatric formulations and adult dosages of 300 mg tablets) should be part of the HIV prevention package for children, adolescents, and adults, including pregnant women and people receiving ART. International funding and drug supply mechanisms such as UNITAID, the Global TB Drug Facility, the US President Emergency Plan for AIDS Relief's Supply Chain Management System, and the AIDS Medicine and Diagnostics Service should

Table 3. Standardized indicators for tuberculosis screening and the provision of isoniazid preventive therapy (adapted from the Guidelines for the monitoring and evaluation of collaborative tuberculosis/HIV activities).

	Intensified TB case-finding among people living with HIV	Proportion of adults and children newly enrolled in HIV care given treatment for latent TB infection (IPT)
Definition	Number of adults and children enrolled in HIV care ^a who had TB status assessed and recorded during their last visit, expressed as a proportion of all adults and children enrolled in HIV care in the reporting period.	Number of adults and children newly enrolled in HIV care ^a who are started on treatment for latent TB infection [isoniazid preventive therapy (IPT)] expressed as a proportion of the total number of adults and children newly enrolled in HIV care over a given time period.
Numerator	Number of adults and children enrolled in HIV care ^a , who had their TB status assessed and recorded during their last visit.	Total number of adults and children newly enrolled in HIV care who start (given at least one dose) treatment of latent TB infection over a given time period.
Denominator	Total number of adults and children enrolled in HIV care ^a in the reporting period.	Total number of adults and children newly enrolled in HIV care over a given time period.
Purpose	This is a process indicator for an activity intended to reduce the impact of TB among people living with HIV. It will demonstrate the level of implementation of the recommendation that people living with HIV are screened for TB at diagnosis and at follow-up visits using their last visit as proxy measure.	To ensure that eligible HIV-positive individuals are given treatment for latent TB infection and thus to reduce the incidence of TB in people living with HIV.
Periodicity	Data are collected continuously and reported as part of the routine cross-sectional reports to national level. These data can be cross-checked during the annual patient monitoring review.	Collected continuously and reported and analyzed quarterly.
Responsibility	National AIDS Control Program.	National AIDS Control Program
Measurement tools	This indicator is collected from the pre-ART and ART registers and summarized on the cross-sectional quarterly reports. This indicator could also be assessed from a systematic sample of patient HIV care/ART cards during annual patient monitoring reviews.	Pre-ART register, aggregated on the cross-sectional quarterly report.

ART, antiretroviral treatment; TB, tuberculosis. Data from [30].

^aHIV care includes HIV treatment, that is, enrollment in the pre-ART register or in the ART register once started on ART.

include INH as a TB prevention commodity for PLHIV as part of their core services.

Establish monitoring and evaluation systems

Functional and integrated monitoring and evaluation systems of IPT implementation that are in line with internationally recommended patient monitoring and evaluation systems [62] and harmonized indicators [30] are essential. Table 3 describes the standardized indicators for TB screening and IPT provision that should be adopted by HIV implementers. The indicator for TB screening measures the number of adults and children enrolled in HIV care (i.e., enrollment in the pre-ART register or in the ART register once started on ART) who had TB status assessed and recorded during their last visit, expressed as a proportion of all adults and children enrolled in HIV care in the reporting period. Even if PLHIV may be screened for TB several times during a given period of reporting, what should be reported is screening in their last contact or visit to the health worker or the facility. The ART and pre-ART registers included in the integrated patient monitoring and evaluation system enable the recording of assessment of TB status on a monthly basis over a 2-year period [62]. Similarly, the IPT indicator measures the number of adults and children newly enrolled in HIV care who are started on treatment with IPT expressed as a proportion of the total number of adults and children newly enrolled in HIV care over a

given time period. This is reported quarterly. Again both pre-ART and ART registers serve as a source for the data. HIV services implementing TB screening and IPT outside the facilities run by the government should embrace these important indicators along with others and set up a reporting mechanism in order to ensure their data are captured to inform the national monitoring and evaluation system. These steps will be useful to address the limitations of the existing data collection system, which may not capture all the implementation of IPT happening out there as the data are primarily coming through the National AIDS and TB Control Programs.

Meaningful engagement of affected communities

National AIDS and TB stakeholders should ensure successful and meaningful engagement of PLHIV and their communities in both planning and implementation of TB screening and IPT. Existing HIV literacy efforts need to mainstream information on TB prevention, diagnosis, and treatment, including TB screening and IPT. Global and national networks of PLHIV need to play a leadership role to ensure the visibility of TB prevention, diagnosis, and treatment services as part of their advocacy work both nationally and at the grass root level. PLHIV and their affected communities should be encouraged to consider IPT as an evidence-based effective intervention and should be empowered to demand IPT during their encounter with HIV service providers.

Conclusion

IPT has been shown to be beneficial for PLHIV, but uptake has been slow for a number of reasons, including resource constraints and reluctance on the part of policy makers and program implementers. With the widespread establishment of HIV care and treatment programs, the opportunity exists to incorporate TB screening using a simple symptom-based clinical algorithm that will reliably identify PLHIV who can commence IPT or who will be investigated for TB or other illnesses. This approach calls for the abolition of the obsolete view of considering IPT as a stand-alone NTP-led TB intervention. IPT is primarily an HIV intervention, which should be a responsibility of National AIDS Programs, any HIV services, and primary care services where PLHIV seek care.

HIV services implementing TB screening and IPT should embrace standardized TB screening and IPT indicators, including the use of standardized pre-ART and ART registers [62]. If the implementation is outside the facilities run by the government, a reporting mechanism should be established in order to ensure data are captured by the national monitoring and evaluation system. Prevention of TB in this population will contribute to the overall goal of reducing global TB burden and improving the quality of life of PLHIV.

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