Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings

World Health Organization

HIV TB

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Department of HIV/AIDS

Stop TB Department

World Health Organization, Geneva, Switzerland

WHO Library Cataloguing-in-Publication Data

Guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource constrained settings.

1.Tuberculosis - prevention and control. 2.Tuberculosis - diagnosis. 3.HIV infections - complications. 4.Isoniazid - therapeutic use. 5.Predictive value of tests. 6.Developing countries. 7.Guidelines. I.World Health Organization. Stop TB Dept. II.World Health Organization. Dept of HIV/AIDS.

ISBN 978 92 4 150070 8 (NLM classification: WF 220)

Edited and proof read by Bandana Malhotra

Printed in Italy

Layout design: www.blossoming.it

www.who.int/hiv/topics/tb/en/index.html

www.who.int/tb/challenges/hiv/en/index.html

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Summary of declarations of interest

All members of the Guidelines Group were asked to complete a World Health Organization (WHO) declaration of interest form and only two declared a conflict of interest. These were discussed within the WHO steering group and then with the Guidelines Group before the deliberations. Alison Grant declared receiving financial support of GB£ 200 from Roche to attend the International AIDS Conference, Sydney, 2007 when the aeroplane she was flying in broke down and the GB£ 200 was paid for a flight deviation. Helen Ayles declared receiving financial support amounting to US$ 15 000 from the Bill and Melinda Gates Foundation, US$ 50 000 from Senter Novum and €150 000 from Delft Imaging Systems to conduct research on intensified TB case-finding and isoniazid preventive therapy for TB, and the development of computer-aided diagnostics for TB/HIV. The Guidelines Group discussed these and concluded that there was no conflict of interest. Declarations of interest were collected from all non-WHO peer reviewers. No peer reviewer declared a conflict of interest. All declarations of interest are on electronic file with the Department of HIV/AIDS of WHO.

Acknowledgements

The development of these guidelines was financially supported by the Joint United Nations Programme on HIV/AIDS Unified Budget and Workplan (UNAIDS UBW) and the US President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) and United States Agency for International Development (USAID).

Contents

Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral (drug)
CDC	Centers for Disease Control and Prevention
CPT	co-trimoxazole preventive therapy
GRC	Guideline Review Committee
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	intensified case-finding
IGRA	interferon-gamma release assay
INH	isonicotinic acid hydrazide/isoniazid
IPT	isoniazid preventive therapy
LTBI	latent tuberculosis infection
MDR	multidrug-resistant (TB, resistant to at least isoniazid and rifampicin)
M&E	monitoring and evaluation
PCR	polymerase chain reaction
PEPFAR	US President's Emergency Plan for AIDS Relief
PMTCT	prevention of mother-to-child transmission (of HIV)
TB	tuberculosis
The Union	International Union Against Tuberculosis and Lung Disease
TST	tuberculin skin test
UNAIDS	The Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development
WHO	World Health Organization
XDR	extensively drug-resistant TB (defined as resistance to at least rifampicin and isoniazid from among the first-line anti-TB drugs, in addition to resistance to any fluoroquinolone, and to at least one of three injectable second-line anti-TB drugs used in TB treatment [capreomycin, kanamicin and amikacin])

Executive Summary

HIV is the strongest risk factor for developing tuberculosis (TB) disease in those with latent or new *Mycobacterium tuberculosis* infection. The risk of developing TB is between 20 and 37 times greater in people living with HIV than among those who do not have HIV infection. TB is responsible for more than a quarter of deaths in people living with HIV. Relatively more women than men were detected to have TB in countries with a prevalence of HIV infection of more than 1%. In response to the dual epidemics of HIV and TB, the World Health Organization (WHO) has recommended 12 collaborative TB/HIV activities as part of core HIV and TB prevention, care and treatment services. They include interventions that reduce the morbidity and mortality from TB in people living with HIV, such as the provision of antiretroviral therapy (ART) and the *Three I's for HIV/TB*: intensified case-finding of TB (ICF), isoniazid preventive therapy (IPT), and infection control for TB.

On 25–27 January 2010, WHO conducted a global policy meeting to review the evidence regarding ICF and IPT, and to reconceptualize the 1998 WHO/Joint United Nations Programme on HIV/AIDS (UNAIDS) Policy on TB prevention. Key questions were identified and a comprehensive review of the available scientific evidence was conducted to formulate the recommendations. The evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. The quality of the evidence was categorized as high (when further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the effect) and low (further research is very likely to have an estimate of effect and is likely to change the estimate). Reports were also commissioned from people living with HIV and affected communities regarding the key questions and the summary of the evidence. After the initial draft was reviewed by the Guidelines Group, the comments were incorporated into a draft that was then sent to over 200 people for peer review. Comments from around 30 internal and external peer reviewers were used to finalize the recommendations. The final recommendations take into consideration the quality of evidence, cost, feasibility, and values and preferences of the community and health-care workers. The recommendations were classified as strong when the guidelines group was confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, and as conditional (weak) when the desirable effects of adherence to a recommendation probably outweigh the effects, but the panel was not confident about these trade-offs. These new guidelines recommend the use of a simplified screening algorithm that relies on four clinical symptoms to identify those eligible for either IPT or further diagnostic work-up for TB and other conditions. Chest radiography is no longer a mandatory investigation before starting IPT. In contrast to the 1998 Policy, the new guidelines strongly recommend at least six months of IPT for children and adults including pregnant women, people living with HIV and those receiving ART, and those who have successfully completed TB treatment. IPT for a duration of 36 months is conditionally recommended in settings with a high transmission of TB among people living with HIV. The revised guidelines also emphasize that a tuberculin skin test (TST) is not a requirement for initiating IPT in people living with HIV. However, in some settings where it is feasible, it can help to identify those who would benefit most from IPT. The guidelines also emphasize that IPT is a core component of HIV prevention and care, and should be the primary responsibility of AIDS programmes and HIV service providers. In addition, the provision of IPT should not be viewed as an isolated intervention for people living with HIV. Rather, it should be part of a TB prevention package along with infection control for TB, ICF and provision of ART.

Key recommendations

1 Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

Strong recommendation, moderate quality of evidence[1]

2 Adults and adolescents living with HIV and screened with a clinical algorithm for TB, and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

Strong recommendation, moderate quality of evidence

3 Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

Strong recommendation, high quality of evidence

4 Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT.[2] IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

Conditional recommendation, moderate quality of evidence[3]

5 TST is not a requirement for initiating IPT in people living with HIV.

Strong recommendation, moderate quality of evidence

6 People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.

Strong recommendation, high quality of evidence

[1] A **strong recommendation** is one for which the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
[2] The considerations for implementation should include the local context such as the epidemiology of TB and HIV, and settings with the highest rates of prevalence and transmission of TB among people living with HIV.
[3] A **conditional recommendation** is one for which the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects and data to support the recommendation are scant. Therefore, the recommendation is only applicable to a specific group, population or setting, or new evidence may result in changing the balance of risk to benefit, or the benefits may not warrant the cost or resource requirements in all settings.

7 Providing IPT to people living with HIV does not increase the risk of developing isoniazid (INH)-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

Strong recommendation, moderate quality of evidence

8 Children living with HIV who do not have poor weight gain,[4] fever or current cough are unlikely to have active TB.

Strong recommendation, low quality of evidence

9 Children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, such children should be offered IPT regardless of their age.

Strong recommendation, low quality of evidence

10 Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.

Strong recommendation, moderate quality of evidence

11 In children living with HIV who are less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.

Strong recommendation, low quality of evidence

12 All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.

Conditional recommendation, low quality of evidence

[4] **Poor weight** gain is defined as reported weight loss, **or** very low weight (weight-for-age less than –3 z-score), **or** underweight (weight-for-age less than –2 z-score), **or** confirmed weight loss (>5%) since the last visit, **or** growth curve flattening,

1. Background and process

1.1 Background

HIV is the strongest risk factor for developing tuberculosis (TB) disease in those with latent or new *Mycobacterium tuberculosis* infection. The risk of developing TB is between 20 and 37 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] Relatively more women than men were detected to have TB in countries with a prevalence of HIV infection of more than 1% [1]. In response to the dual epidemics of HIV and TB, the World Health Organization (WHO) has recommended 12 collaborative TB/HIV activities as part of core HIV and TB prevention, care and treatment services.[3] These include interventions that reduce the morbidity and mortality from TB in people living with HIV, such as the provision of antiretroviral therapy (ART) and the *Three I's for HIV/TB*: intensified case-finding of TB (ICF), isoniazid preventive therapy (IPT) and infection control for TB.[4]

A high rate of previously undiagnosed TB is common among people living with HIV.[5,6] ICF and treatment of TB among people living with HIV interrupts disease transmission by infectious cases,[7,8] reduces morbidity and delays mortality.[9] Most importantly, active screening for TB offers the opportunity to provide preventive therapy for those who do not have symptoms and signs of TB.[10]

IPT is a key public health intervention for the prevention of TB among people living with HIV and has been recommended since 1998 by WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) as part of a comprehensive HIV and AIDS care strategy.[11] It has subsequently been included in a number of WHO guidelines and recommendations. [3,12] However, its implementation has been very slow and has been impeded by several barriers including lack of an accepted approach to exclude active TB disease and restricted access to isoniazid for fear of developing drug resistance. By the end of 2009, globally only 85 000 people living with HIV received IPT.[1] It is not known what proportion of these were children.

In April 2008, WHO convened the *Three I's for HIV/TB* Meeting, which called for a re-conceptualization of the existing WHO/UNAIDS Policy on IPT to reflect new scientific evidence and thinking about HIV and TB prevention, care and treatment, and expedite the implementation of this important intervention in tandem with ICF.[4] Therefore, the objective of these guidelines is to provide guidance for national TB and AIDS programmes by updating existing WHO recommendations with new evidence, taking into consideration the changing context of HIV and TB prevention, treatment and care. The new guidelines focus on facilitating the implementation of IPT and ICF. The guidelines are also intended to highlight and strengthen the leadership role of national AIDS programmes and HIV stakeholders to scale up the implementation of TB screening and provision of IPT among people living with HIV.

1.2 Target audience

The guidelines are aimed at health-care workers providing care for people living with HIV, policy-makers and health programme managers working in the field of HIV /AIDS and TB. These guidelines are also intended for governments, nongovernmental organizations, donors and patient support groups that address HIV and TB.

1.3 Scope

The guidelines present a set of recommendations that will help reduce TB disease in people living with HIV, their families and communities through a combination of screening for TB and provision of IPT. The following eight questions were used to guide the review of the evidence for developing the guidelines.

1. What is the best combination of signs, symptoms and diagnostic procedures (e.g. smear microscopy, radiography, serum-based tests such as interferon-gamma release assays [IGRA]) that can be used as screening tools to determine the eligibility for treatment of latent TB infection (LTBI)?
2. What is the optimal duration and drug regimen (e.g. INH, rifampicin, etc.) for treatment of LTBI to reduce the risk of developing TB among people living with HIV?
3. What is the optimal time to start considering initiation of IPT (i.e. should immune status be considered and should IPT be started with ART)?
4. Should secondary treatment of LTBI be provided for people living with HIV to prevent reinfection or recurrence of TB after successful completion of TB treatment?
5. Does treatment for LTBI among people living with HIV lead to significant development of mono-resistance against the drug(s) used for LTBI treatment?
6. Will low adherence rates to treatment for LTBI be a barrier to the implementation of LTBI treatment among people living with HIV?
7. Is the provision of treatment for LTBI cost-effective?
8. Is the use of tuberculin skin test (TST) feasible in resource-limited settings?

The guidelines include evidence-based recommendations for adults, children and infants, the summary and grading of evidence, implementation issues and key research gaps. In contrast to the 1998 WHO/UNAIDS Policy, these new guidelines reconceptualize ICF and the provision of IPT as integral and interlinked components of quality care for people living with HIV. The revised guidelines recommend the use of an evidence-based, simplified TB screening algorithm that relies on four clinical symptoms to identify those eligible for either IPT or further diagnostic work-up for TB or other diseases. Although a subject of another set of WHO guidelines, screening for TB also allows for improved infection control measures to prevent nosocomial transmission. These guidelines also include recommendations for people living with HIV who are pregnant, on ART and have completed TB treatment. The guidelines will be reviewed and updated in five years according to WHO procedure.[13]

1.4 Process of formulating the guidelines

As part of the Guideline Review Committee (GRC)-recommended process, the WHO HIV/AIDS and Stop TB Departments conducted a global policy meeting on 25–27 January 2010 to review the evidence regarding ICF and IPT, and to reconceptualize the 1998 WHO/UNAIDS Policy on TB prevention (Annexes 1–3). Key questions were identified and a comprehensive review of the available scientific evidence was conducted to formulate the recommendations. A WHO Guidelines Group to review the evidence and formulate the recommendations was established and a comprehensive review of the available scientific evidence for eight key questions (*see above*) was prepared. Systematic literature reviews of studies related to the eight questions among people living with HIV were conducted using PubMed, and various combinations of keywords were used to search for studies related to each question. A search was also conducted for abstracts presented at conferences on TB and lung disease organized by the International Union Against TB and Lung Disease (The Union) and the International AIDS Society between 2000 and 2008. All retrieved titles and abstracts were reviewed for their relevance to the topic in the question. The reference lists of the retrieved studies were also reviewed to identify further studies that met the eligibility criteria. In addition, recognized experts in the field were contacted to identify studies that were not available (e.g. unpublished) in the initial electronic search for each question.

The quality of evidence and strength of recommendation was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[14] In the GRADE assessment process, the quality of a body of evidence is defined as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available

from the evidence are close to the actual effects of interest. The usefulness of an estimate of the effect (of the intervention) depends on the level of confidence in that estimate. The higher the quality of evidence, the more likely a strong recommendation can be made; however, the decision regarding the strength of the evidence also depends on other factors. Although the GRADE evidence assessment process was used for all of the questions, it was not always possible to calculate GRADE profiles for all the questions because there was a lack of data and information to calculate the necessary risk ratios. The initial ranking of the evidence for each question was collectively done by the consultants of the systematic review and members of the WHO Steering Group, which was later presented and discussed by the Guidelines Group.
In the GRADE profiles, the following levels of assessment of the evidence were used:

Evidence level	Rationale
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the effect.
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Reports were also commissioned from people living with HIV and affected communities regarding the key questions and the summary of the evidence (Annex 4). The final recommendations also take into consideration the quality of the evidence, cost, feasibility, and values and preferences of the community, and health-care workers. The Guidelines Group, which included two GRADE methodologists, assessed the evidence along with the risks and benefits of each recommendation, and determined their recommendations and the strength of the evidence. The Group used open voting and discussion to arrive at a consensus for each of the recommendations. After the initial draft was reviewed by the Guidelines Group, the comments were incorporated into a draft that was then sent to over 200 people for peer review. The Coordinators of the process, representing the two technical units of WHO (HIV/AIDS and Stop TB Departments), incorporated comments from around 30 internal and external peer reviewers to finalize the recommendations.

1.5 Strength of recommendations

The strength of the recommendations reflects the degree of confidence of the Guidelines Group that the desirable effects of adherence to the recommendations outweigh the undesirable effects. Desirable effects considered include beneficial health outcomes (e.g. prevention and early diagnosis of TB, reduced TB-related morbidity and mortality), less burden and savings, whereas undesirable effects can include harms, more burden and costs. Burdens considered include the demands of adhering to the recommendations that programmes, patients or caregivers (e.g. family) may have to bear, such as having to undergo more frequent test, taking additional medications or opting for a treatment that has a risk for toxicity.

The recommendations in these guidelines were graded into two categories as follows:

A STRONG RECOMMENDATION is one for which the Guidelines Group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This can be either in favour of or against an intervention.

A CONDITIONAL (WEAK) RECOMMENDATION is one for which the panel concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects, but the panel is not confident about these trade-offs. Reasons for not being confident can include: absence of high-quality evidence, presence of imprecise estimates of benefits or harms, uncertainty or variation regarding how different individuals value the outcomes, small benefits, and benefits that may not be worth the costs (including the costs of implementing the recommendation).

Strength of recommendation	Rationale
Strong	The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional (weak)	The panel concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects. However: • Data to support the recommendation are scant; **or** • The recommendation is only applicable to a specific group, population or setting; **or** • New evidence may result in changing the balance of risk to benefit; **or** • The benefits may not warrant the cost or resource requirements in all settings.

1.6 Adaptation of the guidelines

The guidelines have been developed for a global audience and it is expected that regions and countries will adapt the recommendations to suit their own circumstances. These include consideration of the epidemiology of TB and HIV, and defining settings with the highest rates of prevalence and transmission of TB among people living with HIV (for example, to implement IPT lifelong or for 36 months). The ultimate goal of these adaptations should be to scale up implementation of services for TB screening, prevention and treatment as core functions of HIV prevention, treatment and care services. Depending on the situation of the country, a national consultation process involving all the stakeholders should help ensure the creation of a policy and programme environment that is conducive to implementation. Critical factors that need to be addressed during the national adaptation process include incorporation of TB screening and IPT as core interventions in the treatment and care package for people living with HIV. Other critical functions include the development of standardized operating procedures, access to INH (preferably 300 mg tablets) for HIV service providers and implementers, and establishment of an effective and standardized monitoring and evaluation (M&E) system. The evaluation of the efficacy of the guidelines will be done through the global TB and HIV/AIDS reporting system, which will monitor country and global implementation of IPT and ICF. In addition, WHO and ministries of health, along with key stakeholders, will participate in country-level programme reviews to monitor adaptation and implementation of the guidelines. Feedback from the community and other stakeholders will be used to revise the next edition of the guidelines.

2. Intensified case-finding for and prevention of tuberculosis in adults and adolescents living with HIV

2.1 Screening for TB

Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

STRONG RECOMMENDATION, MODERATE QUALITY OF EVIDENCE

Adults and adolescents living with HIV and screened for TB with a clinical algorithm and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

STRONG RECOMMENDATION, MODERATE QUALITY OF EVIDENCE

All people living with HIV, wherever they receive care, should be regularly screened for TB using a clinical algorithm at every visit to a health facility or contact with a health worker. Screening for TB is important, regardless of whether they have received or are receiving IPT or ART. As part of the guidelines development process, a comprehensive systematic primary patient data meta-analysis, including 12 observational studies involving over 8000 people living with HIV, was used to develop the best screening rule to identify adults and adolescents living with HIV who are unlikely to have active TB disease (Annex 5).[15] The analysis found that the absence of all the symptoms of current cough, night sweats, fever or weight loss can identify a subset of people living with HIV who have a very low probability of having TB disease. This best screening rule has a sensitivity of 79% and a specificity of 50%. At 5% TB prevalence among people living with HIV, the negative predictive value was 97.7% (95%CI 97.4–98.0). This high negative predictive value ensures that those who are negative on screening are unlikely to have TB and hence can reliably start IPT. Therefore, the Guidelines Group recommends that adults and adolescents living with HIV should be screened for TB using a clinical algorithm at every visit to a health facility or contact with a health worker. Those who do not have current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT. This recommendation is applicable for those living with HIV irrespective of the degree of immunosuppression, and for those on ART, those who have previously been treated for TB and pregnant women (Figure 1).

Furthermore, the GRADE assessment of the evidence showed that the addition of abnormal findings on chest radiography to the four-symptom-based rule increases the sensitivity from 79% to 91% with a drop in specificity from 50% to 39%. At a 5% TB prevalence rate among people living with HIV, augmenting the symptom-based rule with abnormal findings on chest radiography increases the negative predictive value by a margin of only 1% (98.7% versus 97.8%). On the other hand, the addition of abnormal chest radiographic findings to the symptom-based rule at a TB prevalence of 20% among people living with HIV increases the negative predictive value by almost 4% (94.3% versus 90.4%). This suggests that chest radiography could be considered to augment the utility of symptom-based screening in settings with high TB prevalence rates among people living with HIV. However, the Guidelines Group recognized that the desire for increased sensitivity and negative predictive value is often accompanied by significant feasibility concerns such as cost, workload, infrastructure and qualified staff. Therefore, the Guidelines Group recommends that in most settings, the symptom-based rule should be implemented,

regardless of the availability of radiography, consistent with the recommended algorithm (Figure 1).

Adults and adolescents living with HIV who have any one of the four symptoms (current cough, fever, weight loss or night sweats) may have active TB and should be evaluated for TB and other diseases. The diagnostic work-up for TB should be done in accordance with national guidelines and sound clinical practice to identify either active TB or an alternative diagnosis.

2.2 Efficacy, regimen and duration

Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

Strong recommendation, high quality of evidence

Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least 36 months of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

Conditional recommendation, moderate quality of evidence

2.2.1 Efficacy

The Guidelines Group reviewed the available evidence regarding the benefit of chemotherapy to prevent TB disease (latent disease, reactivation or reinfection) in adults living with HIV (Annex 6). A GRADE assessment was used to examine the existing evidence on drug regimens including the 12 randomized controlled trials used in the Cochrane review of preventive therapy.[16] For those with confirmed, probable or possible TB disease, preventive chemotherapy reduces the overall risk of developing TB by 33% (relative effect 0.67; CI 0.51–0.87). For those who were TST positive, the reduction in confirmed, probable or possible TB increased to 64% (RR [95% CI] 0.36 [0.22–0.61]). Although not statistically significant, the reduction among TST-negative persons was 14% (RR [95% CI] 0.86 [0.59, 1.26]) and in those with unknown TST status it fell by 14% (RR [95% CI] 0.86 [0.48, 1.52]).[16] The Guidelines Group concluded that there is benefit in providing TB preventive therapy to people living with HIV regardless of the TST status, with greater protective benefit seen in those with a positive TST.

2.2.2 Regimen and duration

The Guidelines Group reviewed the evidence on a wide range of regimens used for TB prevention and their duration among people living with HIV, including results from three unpublished trials (Annex 6). The Group reviewed studies of the drug combinations used for prevention including INH, rifampicin, pyrazinamide and rifapentine. A total of eight studies compared INH alone with other regimens, and found that regimens that included pyrazinamide, rifampicin and rifapentine were as efficacious as INH alone, but were associated with higher rates of toxicity (Table 1). The Guidelines Group concluded that INH at 300 mg/day remains the drug of choice for chemotherapy to prevent TB in adults living with HIV.

The Guidelines Group also reviewed the evidence on the duration and durability of effect of IPT in people living with HIV. The critical outcomes of interest considered were the efficacy of IPT in preventing active TB, relapse, reinfection and toxicity.

2.2.2.1 Table 1: Comparison of the efficacy of different drug regimens

Intervention	Comparator	RR (95% CI)	Quality of evidence
INH	Rifampicin and pyrazinamide	1.03 (0.75–1.4)	Moderate
INH	INH and rifampicin	0.97 (0.52–1.83)	Moderate
INH	INH, rifampicin and pyrazinamide	0.69 (0.23–1.57)	Low
INH and rifampicin	INH, rifampicin and pyrazinamide	0.75 (0.21–1.82)	Moderate
INH and rifapentine	INH	1.05 (0.56–1.97)	Moderate

The Guidelines Group considered the existing evidence on the optimal duration of IPT including for six, nine, 12 and 36 months (Annex 6). The evidence primarily focused on the comparison of a six- and 12-month duration of IPT, and found no significant difference in efficacy.[16] Although nine months of IPT is supported by evidence and recommended in some guidelines, there are no studies that have directly compared IPT for six and nine months. This led the Guidelines Group to strongly recommend the six-month duration. The protective effect of IPT decreases with time and the durability ranges for up to five years. The Guidelines Group reviewed emerging unpublished evidence from two clinical trials that suggest increased benefit with a 36-month or longer duration of IPT, particularly in people who are TST positive.[17,18] Given that longer trials are expensive and unlikely to be done, the Guidelines Group considered a duration of at least 36 months as a surrogate for lifelong treatment. It also emphasized the potential benefit of extended IPT for people living with HIV in settings with a background of high HIV and TB prevalence and transmission. Given the preliminary and scanty nature of the evidence, feasibility concerns and potential adverse events, the Guidelines Group conditionally recommends 36 months' duration of IPT for people living with HIV in settings with high TB prevalence and transmission, as determined by the local context and national guidelines.

2.2.3 Immune status and concomitant use of IPT with ART

The Guidelines Group reviewed available data regarding the initiation of IPT and immune status, including concomitant use with ART. Six studies were examined which showed contrasting results regarding the reduction of TB risk by immune status (Annex 6). Additional protective benefits of concomitant use of IPT with ART were demonstrated in two observational studies from Brazil [19] and South Africa,[20] and a sub-analysis of data from an unpublished randomized clinical trial from Botswana.[17] Based on this evidence and the potential benefit of concomitant use of IPT with ART, the Guidelines Group strongly recommends that IPT be given irrespective of immune status and whether or not a person is on ART. IPT initiation or completion should not be the cause for a delay in starting ART for eligible people living with HIV.[21] However, the Guidelines Group recognizes the absence of evidence on whether concomitant initiation of IPT with ART or delayed initiation of IPT is better in terms of efficacy, toxicity or the development of immune reconstitution.

2.2.4 Pregnant women

Pregnant women living with HIV are at risk for TB, which can impact on maternal and perinatal outcomes.[22] These could range from death of the mother and the newborn, to prematurity and low birth weight of the newborn. [23] The Guidelines Group stressed the importance of screening pregnant women living with HIV for active TB using the clinical algorithm as mentioned above. This implies the introduction of the clinical algorithm into maternal HIV services in order to prevent, diagnose and treat TB. The Group concluded that evidence and experience from the pre-HIV and HIV era suggest that IPT is safe in pregnant women. Therefore, the Guidelines Group strongly recommends that pregnancy should not exclude women living with HIV from symptom-based TB screening and receiving IPT. However, sound clinical judgement is required for decisions such as the best time to provide IPT to pregnant women.

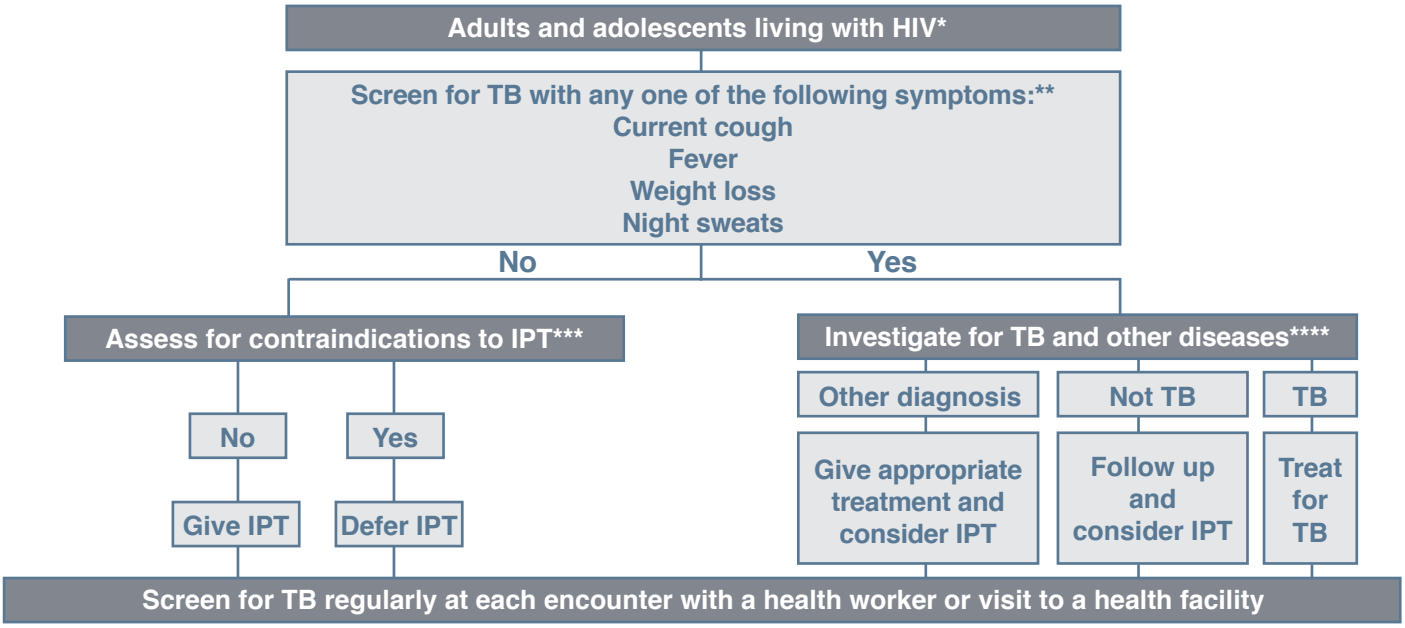
2.2.5 Patients previously treated for TB (secondary prophylaxis)

The Guidelines Group reviewed the evidence and discussed IPT as secondary prophylaxis for people who have previously been successfully treated for TB. GRADE assessment of the evidence from four studies including three randomized controlled trials [24–26] and one observational study [27] showed the value of providing IPT immediately after successful completion of TB treatment (Annex 7). The Guidelines Group strongly recommends that adults and adolescents living with HIV who successfully complete their TB treatment should continue receiving INH for another six months and should conditionally receive it for 36 months based on the local situation (e.g. high rates of TB prevalence and transmission) and existing national guidelines. There was no evidence on the potential role of IPT for those who had successfully completed treatment for multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB. Therefore, the Guidelines Group did not make any recommendation on the use of IPT after successful treatment for MDR or XDR TB.

2.2.6 Special populations

People living with HIV in congregate settings, such as prisons and centres for refugees or internally displaced persons, have a higher risk for and incidence of TB, HIV infection and drug use.[2] Special attention has to be paid to ensure screening for TB and provision of IPT for these groups. Injecting drug users have a higher risk of coinfections with HIV, TB and hepatitis causing viruses. Screening for TB and providing IPT for injecting drug users should be combined with harm reduction measures, including the provision of testing for hepatitis B and hepatitis C infection, and referral for positive cases. [28] Sound clinical judgement is required to weigh the benefits of IPT among injecting drug users with hepatitis coinfection. IPT should not be provided in the presence of active hepatitis.

2.2.7 Figure 1. Algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



FOOTNOTES TO ALGORITHM FOR ADULTS

* Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce *M. tuberculosis* transmission in all settings that provide care.

** Chest radiography can be done if available, but is not required to classify patients into TB and non-TB groups. In high HIV-prevalence settings with a high TB prevalence among people living with HIV (e.g. greater than 10%), strong consideration must be given to adding other sensitive investigations.

*** Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption, and symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for starting IPT. Although not a requirement for initiating IPT, TST may be done as a part of eligibility screening in some settings.

**** Investigations for TB should be done in accordance with existing national guidelines.

2.3 Detecting latent TB infection in resource-constrained settings

2.3.1 Tuberculin skin test (TST) and IPT

TST is not a requirement for initiating IPT in people living with HIV.

Strong recommendation, moderate quality of evidence

People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.

Strong recommendation, high quality of evidence

TST relies on a competent immune response to identify people with latent *Mycobacterium tuberculosis* infection. Multiple studies in people living with HIV demonstrate that IPT is more effective in people with a positive TST than in those with a negative test.[16] In addition, the use of TST could reduce the number of patients receiving IPT and the numbers needed to treat to prevent one case of active TB. However, in resource-constrained settings, operational challenges to the implementation of TST are significant impediments for access to IPT. Such challenges include the costs of procuring tuberculin and administering the test, maintaining an effective supply chain, training staff in administering and accurately reading the test, and the need for the patient to attend the clinic at least twice over 48–72 hours with its associated inconvenience and cost.[29] In addition, the immunological status of the patient and the negative results in anergic patients or those with a long lapse between infection and the TST may affect its interpretation.[30,31] Although some studies suggest that using TST is cost-effective, there is a limited supply of tuberculin worldwide, it is costly to ship and requires an adequate cold chain to ensure accurate test performance (*see* Annex 8).

The Guidelines Group strongly recommends that in resource-constrained settings, TST should not be a requirement for initiating IPT for people living with HIV. People living with HIV whose TST status is unknown should be started on IPT after symptom-based screening for TB. However, given that TST-positive patients benefit more from IPT than those who are TST negative, the test can be used where feasible. People living with HIV who are TST negative should be assessed on a case-by-case basis for their individual risk of TB exposure and the added advantage of the provision of IPT (e.g. health-care workers, prisoners, miners and others who live in a high TB transmission setting). In settings where TST is not available, the Guidelines Group encourages national programmes to explore its expanded use as a potential adjunct to enhancing IPT implementation.

2.3.2 Interferon-gamma release assays (IGRA)

The Guidelines Group discussed the GRADE assessment of the evidence on the use of IGRA as a screening tool to identify patients with latent TB infection (Annex 9). Two types of IGRA were considered: Quantiferon Gold in tube assay and T-Spot assay. Two studies considered the ability of IGRA to predict development of TB over time.[32,33] Eight studies evaluated the performance of Quantiferon Gold in tube assay among HIV-infected adults with confirmed TB, and one study evaluated its sensitivity among children living with HIV diagnosed with TB. Similarly, five studies reported the sensitivity of a T-Spot assay among adults living with HIV and TB, and two studies reported its sensitivity among children living with HIV with confirmed TB.

However, IGRA cannot generally distinguish between active TB disease and latent infection [34] and their performance is compromised among people living with HIV compared to those without HIV. Significantly higher rates of indeterminate test results were found with Quantiferon gold in tube test in persons with HIV compared to persons without HIV, and in persons with low CD4 cell counts compared to persons with higher CD4 cell counts. Its sensitivity was also markedly reduced among patients with low CD4 counts. Similarly, while most studies found no impact of low CD4 cell count on the sensitivity of T-Spot assay, at least one study found that sensitivity was significantly reduced among patients with low CD4 counts.

The Guidelines Group noted that the data suggesting the use of IGRA to identify latent TB in persons living with HIV are restricted to studies conducted in low TB-prevalence settings and there is no evidence that IGRA will determine who will benefit most from IPT. Based on the available data, the Guidelines Group concluded that IGRA are not recommended to screen people living with HIV for eligibility to receive IPT.

2.4 Issues to consider for implementation of IPT

2.4.1 Primary ownership by HIV service providers

HIV treatment and care services should include a comprehensive approach to preventing, diagnosing and treating TB with an emphasis on the *Three I's for HIV/TB*. The Guidelines Group concluded that providing IPT as a core component of HIV preventive care should be the responsibility of national AIDS programmes and HIV service providers. In addition, IPT should not be viewed as an isolated intervention and should be part of a TB prevention package along with infection control for TB, ICF and the provision of early ART to those with CD4 counts <350 cells/mm^3 (people with TB should receive ART irrespective of CD4 count). National AIDS programmes and providers of HIV services should ensure the meaningful engagement of people living with HIV, persons with TB and their communities in both the planning and implementation of these interventions.[35]

The implementation of TB screening and IPT needs to be monitored and evaluated through established and recommended patient M&E systems [36] that should use internationally recommended indicators. [37] HIV stakeholders implementing TB screening and IPT in resource-limited settings outside of the facilities run by the government should ensure that a reporting mechanism is established so that their data are captured in one national M&E system.

2.4.2 IPT and drug-resistant TB

Providing IPT to people living with HIV does not increase the risk of developing INH-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

Strong recommendation, moderate quality of evidence

One of the reasons commonly cited for not offering IPT to people living with HIV is the fear of developing drug-resistant TB. The Guidelines Group reviewed the evidence on the provision of IPT and drug-resistant TB, which was presented after GRADE assessment of the evidence (Annex 10). This included eight studies and the results of a meta-analysis which concluded that INH resistance is not significantly associated with the provision of IPT.[38] The GRADE assessment of the evidence examined the relative risk of developing INH-resistant TB among all of those receiving isoniazid and found no statistically significant increased risk of resistance (RR 95% CI= 1.87 [0.65–5.38]). In addition, the results of a study that was under publication and showed no risk of development of drug resistance after provision of IPT to gold miners were also presented and discussed.[39] The Guidelines Group also noted that regular TB screening for those taking IPT will help identify those who could develop TB as early as possible. This early identification will allow for prompt diagnosis and treatment, which should also help to prevent the development of drug-resistant TB. The Guidelines Group noted that in settings with high INH resistance, fewer patients are likely to benefit from IPT, and the decision to provide access to IPT for people living with HIV should thus be based on the local context. Programmes implementing IPT are encouraged to introduce international and national TB drug-resistance surveillance systems that also include HIV testing as an integral component.

2.4.3 Adherence and clinical follow up

The Guidelines Group reviewed the evidence regarding the importance of adherence to IPT (Annex 11). The available data were observational and did not directly address whether poor adherence adversely affects individual or programme outcomes. Adherence rates for IPT

varied widely from 34% to 98%, and a number of factors were identified to improve adherence.[40–44]

The Guidelines Group noted that, although treatment completion is important for good individual and programme outcomes, the primary objective should be to ensure that people do not continue to take IPT in the rare instance of active TB or development of toxicity. People living with HIV and receiving IPT should have regular clinical follow up based on the national, local and clinical context. This includes regular screening using the TB symptom-based rule during every contact with a health-care provider. The Guidelines Group noted that the co-formulation of INH with other drugs (e.g. ART or CPT) could reduce the pill burden and enhance adherence, and called for expedited development of such co-formulations. The Guidelines Group strongly recommends that concerns regarding adherence should not be a barrier to implementing IPT.

2.4.4 Cost-effectiveness of IPT

The Guidelines Group concluded that the available data on the cost-effectiveness of IPT is of low quality with significant variability between outcome measures, assumptions and analytical procedures (Annex 12). It was recognized that this is an area that requires additional research to better inform programmatic decision-making. However, after a review of the evidence, the Guidelines Group strongly recommends that the provision of IPT is likely to be cost-effective. This supports the overall recommendation for the wide use of IPT within comprehensive HIV prevention, care and treatment services, both as a measure of good clinical practice and as a likely cost-effective measure.

3. Intensified tuberculosis case-finding and prevention of tuberculosis in children living with HIV

3.1 Screening for TB

Children living with HIV who do not have poor weight gain,* fever or current cough are unlikely to have active TB.

Children living with HIV who have any one of the following symptoms – poor weight gain*, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of their age.

* Poor weight gain is defined as reported weight loss, **or** very low weight (weight-for-age less than –3 z-score), **or** underweight (weight-for-age less than –2 z-score), **or** confirmed weight loss (>5%) since the last visit, **or** growth curve flattening.

Strong recommendations, low quality of evidence

Encouraging efforts have been made to expand access to early diagnosis of HIV in children as part of HIV prevention, care and treatment. TB screening, prevention and treatment should be an integral part of these services. This section of the guidelines is specifically targeted at children living with HIV. However, in circumstances where HIV-exposed infants and children are receiving HIV care pending a result of a virological or serological test, they should be considered as children living with HIV and get the appropriate services until their results are known.

For infants less than 6 weeks of age and unknown HIV exposure, and in settings where the HIV epidemic is generalized (i.e. >1% prevalence in the population attending antenatal care services), programmes are strongly recommended to provide HIV serological testing to mothers or their infants in order to establish exposure status. Virological testing should be conducted at 4–6 weeks of age for infants known to be exposed to HIV, or at the earliest possible opportunity for those seen after 4–6 weeks of birth. For children 12–18 months of age, diagnosis using virological testing is recommended. However, in resource-constrained settings where access to virological testing is limited, it is recommended that, for this age group, virological tests be performed only after positive serological testing. A definitive diagnosis of HIV in children aged 18 months or more (with known or unknown HIV exposure) can be made with HIV serological tests, including rapid serological tests following standard testing algorithms used for adults.[45]

The Guidelines Group stressed that infants and children living with HIV should routinely be screened for TB as a part of standard clinical care, whether they are receiving TB prophylaxis or ART. However, the diagnosis of TB in children, with or without HIV, is difficult and clinicians need a high index of suspicion at all times and should follow national guidelines. A history of contact of the infant or child with someone with TB (regardless of the type of TB disease) within the home is particularly important and should motivate the health-care worker to screen for TB in the child and among the other family members.

Based on this analysis and the relative lack of good studies, the Guidelines Group concluded that the quality of evidence is low and available data are limited regarding the best approach to screening infants and children for TB. The range of evidence assessed using GRADE included a number of scoring systems for children who are not infected with HIV. However, such scoring systems were not found to be as effective in children living with HIV (Annex 13).[46] The evidence also included one unpublished study that investigated a combination of signs and symptoms to reliably exclude active TB in a child with HIV. The

study showed that the absence of cough of more than two weeks' duration, fever and failure to thrive could identify children unlikely to have active TB with a 99% negative predictive value. Such children would therefore be eligible for IPT. Similarly, the presence of cough for more than two weeks, or failure to thrive or fever has a sensitivity of 90% and specificity of 65%, and is therefore useful for identifying children in need of further screening for TB or alternative diagnoses. [47] Another study among 1024 children suggested that weight loss and cough for more than two weeks and fatigue had a sensitivity of only 56% and specificity of 62%.[48]

In order to facilitate programmatic implementation and increase the likelihood of identifying children without active TB for IPT, the Guidelines Group recommends that the duration of cough as a screening rule should be reduced to the presence of any current cough, in line with the recommendation for adolescents and adults. Unlike the screening rule for adults and adolescents, this recommendation is based on expert opinion and clinicians need to broaden the differential diagnosis to include other diseases that may cause children with HIV to present with current cough, fever and poor weight gain. Similarly, contact history with a known TB case should raise the clinical suspicion of TB in children living with HIV.

The Guidelines Group recommends that children living with HIV without poor weight gain, fever and current cough are unlikely to have active TB and should be offered IPT (*see below* for age-specific recommendations). Similarly, children living with HIV with any one of the following symptoms – *poor weight gain*, fever, current cough and contact with a TB case – may have TB and should be evaluated for TB and other diseases. If the evaluation shows no TB, such children should be offered IPT regardless of their age (Figure 2).

3.2 Regimen and duration

Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.

In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.

Strong recommendations, moderate quality of evidence

All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.

Conditional recommendation, low quality of evidence

Two studies were considered for the GRADE assessment of the evidence (Annex 14). One study suggested considerable benefits for children receiving INH for six months, in particular, with regard to significant reductions in mortality.[49] However, findings from a randomized control trial conducted in South Africa showed that when HIV-infected infants with no known exposure to a TB source case are identified in the first three to four months of life, given rapid access to ART and carefully monitored for new TB exposure or disease on a monthly basis, there is no benefit from IPT (Madhi 2008, unpublished).

Therefore, based on this, the Guidelines Group recommends that all children living with HIV who are more than 12 months of age and who are unlikely to have active TB should receive six months of IPT as part of a comprehensive package of HIV care. For those children less than 12 months of age, only those who have been evaluated for TB (using investigations) should receive six months IPT if the evaluation shows no TB disease. In contrast to adults and adolescents, there is no evidence to support the use of INH for longer than six months in children. Therefore, the Guidelines Group concluded that until more data are available, INH for children could not

be recommended for more than six months. Similarly, there is no evidence on whether repeating a course of IPT is beneficial for children.

INH should be given at a dose of 10 mg/kg body weight and it is desirable that vitamin B6 be supplied with INH at a dose of 25 mg daily. All available data to date suggest that INH is not toxic for children, even in those receiving ART. The following table shows a simplified dosing schedule for children (total dose 10 mg of INH/kg/day).

Weight range (kg)	Number of 100 mg tablets of INH to be administered per dose (total dose 10 mg/kg/day)	Dose given (mg)
<5	½ tablet	50
5.1–9.9	1 tablet	100
10–13.9	1 ½ tablet	150
14–19.9	2 tablets	200
20–24.9	2 ½ tablets	250
>25	3 tablets or one adult tablet	300

3.3 Secondary prophylaxis and IPT with ART in children

3.3.1 Secondary prophylaxis

The Guidelines Group noted that there is no evidence on the use of IPT in children living with HIV after successful completion of TB treatment. However, like adults, children living with HIV are exposed to reinfection and recurrence of TB. Therefore, the Group conditionally recommends that all children living with HIV who have been successfully treated for TB and are living in settings with a high TB prevalence and transmission should receive IPT for an additional six months. IPT can be started immediately after the last dose of anti-TB therapy or at a later date. TB screening should be carried out for all children living with HIV, regardless of history of TB treatment, during each contact of the child with a health-care worker (Annex 13).

3.3.2 IPT with ART in children

The Guidelines Group concluded that there are no data regarding the efficacy of IPT for children stratified by degree of immunosuppression. However, it was noted that there is biological plausibility in extrapolating what is known for adults and adolescents to children. Therefore, the Guidelines Group conditionally recommends the combined use of IPT with ART for all children. The Guidelines Group also emphasized that ART should not be delayed while starting or completing a course of IPT.[45]

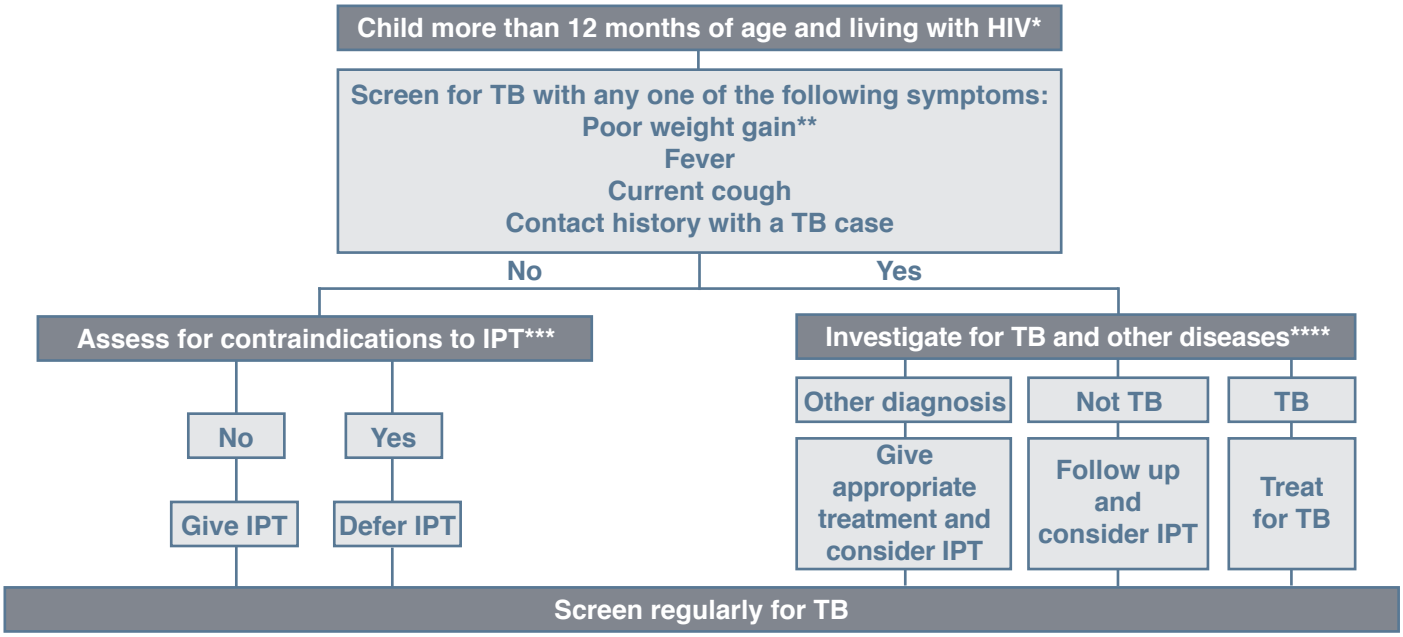
3.4 The role of TST and IGRA in evaluating children for IPT

The Guidelines Group, as in the recommendation for adults, concluded that TST is not required to initiate IPT in children and should not be routinely used as part of the process to determine eligibility for IPT (Annex 9). However, the Group noted that TST may provide important additional information in assessing a child with suspected TB, especially if there is no positive contact history. Although a positive TST may indicate infection with mycobacteria, usually *Mycobacterium tuberculosis*, it is not a reliable marker of TB disease activity. The main limitation of TST in the diagnosis of TB in HIV-infected children is its variable sensitivity. Important clinical causes of false-negative results include severe malnutrition, severe TB disease and HIV infection. Therefore, in settings where it is available, TST may be used for the diagnosis of active TB in children and may also have a role in screening for LTBI.

Like TST, IGRA cannot distinguish between *M. tuberculosis* infection and active TB disease.

Encouraging data show that IGRA are more sensitive than TST in HIV-infected children, including those with a low CD4 count and/or malnutrition.[50–52]. In addition, excellent specificity for *M. tuberculosis* infection has been reported and, unlike TST, IGRA are unaffected by prior BCG vaccination or exposure to environmental mycobacteria. However, more evidence is needed and implementation issues affecting most HIV-prevalence settings (cost, specific laboratory equipment and the need for a venous blood sample) have to be addressed. Therefore, the Guidelines Group strongly recommends that there is currently insufficient evidence to support the use of IGRA to identify children eligible for IPT outside research settings with laboratory-validated procedures.[53]

3.5 Figure 2: Algorithm for TB screening in children more than one year of age and living with HIV



FOOTNOTES TO ALGORITHM FOR CHILDREN

* All children and infants less than one year of age should be provided with IPT if they have a history of household contact with a TB case.

** Poor weight gain is defined as reported weight loss, **or** very low weight (weight-for-age less than –3 z-score), **or** underweight (weight-for-age less than –2 z-score), **or** confirmed weight loss (>5%) since the last visit, **or** growth curve flattening.

*** Contraindications include: active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. Past history of TB should not be a contraindication for starting IPT. Although not a requirement for initiating IPT, TST may be done as a part of eligibility screening in some settings.

**** Investigations for TB must be done in accordance with existing national guidelines.

4. Research gaps

The review of the evidence for formulating the recommendations exposed important unmet research needs (Annex 15). The Guidelines Group discussed the priority research gaps that need to be addressed in order to update these guidelines. The following are the key questions identified by the Guidelines Group in all the areas included in these guidelines. It is imperative that research, donors and the scientific community expedite the implementation of research to respond to these gaps in order to inform policy formulation and programme implementation. Along with global TB and HIV stakeholders, WHO has developed a document that summarizes the overall research priorities around TB/HIV and addresses the broader context of research gaps.[54]

4.1 Screening for TB

- A new point-of-care test is needed to identify active TB, LTBI and those not infected with *M. tuberculosis*; particular emphasis should be placed on new diagnostics for children.
- The role of IGRA in people living with HIV who are infected with *M. tuberculosis* with or without active TB; information is needed about the association between performance of IGRA and immune status.
- The use of TST testing in people living with HIV and receiving ART, with a particular emphasis on the frequency of performing TST to determine immune reconstitution and/or boosting in those who were initially TST negative.
- What is the optimal TB screening algorithm to be used across different settings with different TB and HIV disease burdens to safely initiate preventive therapy.
- The optimal frequency of screening people with HIV for active TB with a symptom-based questionnaire.
- Evaluation of the WHO-recommended algorithm to diagnose TB using new technological advances such as LED microscopy, rapid culture and polymerase chain reaction (PCR)-based methods
- Further validation of the screening algorithm in various programmatic settings.
- Effect of ICF on nosocomial transmission, in particular, among people living with HIV, health-care workers and/or their families.
- Optimal diagnostic algorithm for diagnosis of TB following TB screening for IPT.

4.2 Preventive treatment for TB

- Optimal duration, safety, efficacy and cost-effectiveness of IPT alone or in conjunction with ART in reducing the risk of active TB, compared to ART alone among people living with HIV, particularly under programme conditions.
- Co-formulation as a fixed-dose combination of isoniazid and vitamin B6 with co-trimoxazole, and with antiretrovirals, and evaluation of the efficacy and effectiveness of such fixed-dose combinations.
- Further evaluate the role of vitamin B6 in people living with HIV.
- Evaluate the efficacy and feasibility of long-term IPT in children.
- Study the efficacy of IPT in people with HIV and hepatitis C virus (HCV) coinfection.
- Determine the best regimen for and approach to IPT for those with drug-resistant or suspected to have drug-resistant *M. tuberculosis*.
- Outcomes of TB treatment for “breakthrough TB” in people living with HIV.
- Optimal timing for initiation of IPT in relation to initiation of ART.
- For those on lifelong IPT, is there value in discontinuing it after immune reconstitution?
- Interaction between IPT and other medications, particularly in the context of coinfection with viral hepatitis.
- Modelling studies to estimate the risks and benefits of IPT – key considerations include the incidence and prevalence of HIV and TB, risk for TB by immune status, impact of ART on prevention of both HIV and TB, added benefit of IPT, optimum duration of IPT, prevalence of INH and rifampicin resistance, immune status, TST status.

4.3 Operational research

- Potential limitations of IPT in populations with a high prevalence of INH-resistant TB.
- Risks and benefits of administering INH (in error) to undiagnosed people with active TB.
- Effectiveness of IPT programmes in resource-limited settings; cost-effectiveness and cost–benefit from the health systems and patients' perspectives.
- IPT and special populations: benefits of and duration for health-care workers living with HIV; frequency of screening; benefits for TST-negative health-care workers; HIV-exposed children.
- How to operationalize short-term and lifelong IPT with a particular focus on monitoring programmes and individuals (i.e. clinical status and adherence).
- Population-based drug-resistance surveillance to determine the impact of IPT programmes on drug-resistant TB in the community, including increases or decreases in mono-INH and mono-rifampicin resistance, and MDR TB.
- Evaluate the best national programmes or services to lead the implementation of IPT (e.g. HIV, maternal and child health [MCH], TB, all programmes).
- Optimal delivery of IPT and other HIV care for special groups including women and children.

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6. Selected GRADE profiles

GRADE profile table 1: TB screening for adults and adolescents

What is the best combination of symptoms with or without radiology that can be used as a screening tool to identify people living with HIV who are eligible for treatment of LTBI and for diagnostic work-up for active TB?

Bibliography: Ayles et al. 2009; Corbett et al. 2010; Cain et al. 2010; Corbett et al. 2007; Lewis et al. 2009; Shah et al. 2009; Kimerling et al. 2002; Lawn et al. 2009; Chheng et al. 2008; Getahun et al. (in press)

Any one of current cough, fever, night sweats, weight loss as the best combination of symptoms for screening			
Values and uncertainty around these	Number of participants (studies)	Quality of evidence	Importance
Negative predictive value			
0.97 (95% CI: 0.97, 0.98)	8148 (9 studies)	Moderate	Critical
Sensitivity			
0.79 (95% CI: 0.75, 0.82)	8148 (9 studies)	Moderate	Critical
Specificity			
0.49 (95% CI: 0.29, 0.70)	8148 (9 studies)	Moderate	Important
Any one of current cough, fever, night sweats, weight loss or abnormal chest X-ray findings as the best combination of symptoms for screening			
Negative predictive value			
0.98 (95% CI: 0.97, 0.99)	2805 (4 studies)	Moderate	Critical
Sensitivity			
0.90 (95% CI: 0.66, 0.97)	2805 (4 studies)	Moderate	Critical
Specificity			
0.38 (95% CI: 0.12, 0.73)	2805 (4 studies)	Moderate	Important

GRADE profile table 2: TB screening for children

What is the best combination of symptoms and diagnostic tools that can be used as a screening tool to identify HIV-infected children eligible for treatment of LTBI?

Bibliography: Song et al. 2009

Quality assessment							
Quality assessment	Design (number of participants)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence
Any one of cough ≥2 weeks, fever or failure to thrive							
Negative predictive value 0.99							
1	Observational study (303)	Serious limitation*	No serious inconsistency	No serious indirectness	No serious imprecision#		Low
Sensitivity 0.90							
1	Observational study (303)	Serious limitation*	No serious inconsistency	No serious indirectness	No serious imprecision#		Low
Specificity 0.65							
1	Observational study (303)	Serious limitation*	No serious inconsistency	No serious indirectness	No serious imprecision#		Low
Positive predictive value 0.15							
1	Observational study (303)	Serious limitation*	No serious inconsistency	No serious indirectness	No serious imprecision#		Low

A combination of culture and radiological appearance was used as a gold standard, which is not a perfect gold standard. The study did not qualify for the highest quality of evidence since it was an observational study and did not have a well-defined gold standard.
* The reference standard used is unlikely to correctly classify all the children with disease as having the disease. Moreover, sputum was collected only from children having signs and symptoms suggestive of TB or abnormal chest X-ray findings.
# Confidence intervals for sensitivity and specificity were not reported.

GRADE profile table 3: Efficacy of INH vs placebo in persons with any TST status

Bibliography: Pape et al. 1993; Whalen et al. 1997; Hawken et al. 1997; Mwinga et al. 1998; Fitzgerald et al. 2001; Gordin et al. 1997; Rivero et al. 2003; Whalen et al.1997 – anergy

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Active TB incidence (probable, possible, confirmed) (follow up 1-3 years; clinical examination, chest X-ray, sputum for AFB)						
8	Randomized trials	No serious limitations	No serious inconsistency[1]	No serious indirectness	No serious imprecision	None
Confirmed TB (follow up 1-3 years; culture-proven)						
5	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None
Mortality (any cause) (follow up 1-3 years; review of hospital records)						
7	Randomized trials	No serious limitations	Serious[2]	No serious indirectness	No serious imprecision	None
HIV disease progression (follow up 1-3 years; clinical and immunological criteria)						
2	Randomized trials	No serious limitations	Serious[2]	No serious indirectness	No serious imprecision	None
Adverse drug reaction leading to treatment interruption (follow up 1-3 years; clinical and laboratory monitoring)						
7	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None

[1] Three out of 8 studies showed an opposite direction of the effect

[2] Different direction of the effect across the studies

Summary of findings					
No. of patients		Effect		Quality	Importance
INH prophylaxis	Control	Relative risk (95% CI)	Absolute		
85/2152 (3.9%)	123/1984 (6.2%)	RR 0.67 (0.51–0.87)	20 fewer per 1000 (from 8 fewer to 30 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
	2%		7 fewer per 1000 (from 3 fewer to 10 fewer)		
	50%		165 fewer per 1000 (from 65 fewer to 245 fewer)		
34/1037 (3.3%)	123/1984 (6.2%)	RR 0.72 (0.47–1.11)	13 fewer per 1000 (from 24 fewer to 5 more)	⊕⊕⊕⊕ HIGH	CRITICAL
	2%		6 fewer per 1000 (from 11 fewer to 2 more)		
	50%		140 fewer per 1000 (from 265 fewer to 55 more)		
427/2152 (19.8%)	419/1984 (21.1%)	RR 0.95 (0.85–1.06)	11 fewer per 1000 (from 32 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
	5%		3 fewer per 1000 (from 7 fewer to 3 more)		
	50%		25 fewer per 1000 (from 75 fewer to 30 more)		
41/184 (22.3%)	43/171 (25.1%)	RR 0.88 (0.6–1.28)	30 fewer per 1000 (from 101 fewer to 70 more)	⊕⊕⊕O MODERATE	CRITICAL
	10%		12 fewer per 1000 (from 40 fewer to 28 more)		
	50%		60 fewer per 1000 (from 200 fewer to 140 more)		
56/2026 (2.8%)	33/1873 (1.8%)	RR 1.66 (1.09–2.51)	12 more per 1000 (from 2 more to 27 more)	⊕⊕⊕⊕ HIGH	CRITICAL
	0%		0 more per 1000 (from 0 more to 0 more)		
	20%		132 more per 1000 (from 18 more to 302 more)		

GRADE profile table 4: Efficacy of INH vs placebo in persons who are TST positive

Bibliography: Pape et al. 1993; Whalen et al. 1997; Hawken et al. 1997; Mwinga et al. 1998

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Active TB incidence (probable, possible, confirmed) (follow up 1-3 years; clinical examination, chest X-ray, sputum for AFB)						
4	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None
Confirmed TB (follow up 1-3 years; culture-proven)						
1	Randomized trials	No serious limitations	Serious[1]	No serious indirectness	Serious[2]	None
Mortality (any cause) (follow up 1-3 years; review of hospital records)						
3	Randomized trials	No serious limitations	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None
HIV disease progression (follow up 1-3 years; clinical and immunological criteria)						
1	Randomized trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None

[1] Only one study available to address this outcome
[2] Small sample size and wide CI
[3] Mwinga et al. report an opposite direction of the effect

Summary of findings					
No. of patients		Effect		Quality	Importance
INH prophylaxis	Control	Relative risk (95% CI)	Absolute		
18/693 (2.6%)	46/618 (7.4%)	RR 0.36 (0.22–0.61)	48 fewer per 1000 (from 29 fewer to 58 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
	2%		13 fewer per 1000 (from 8 fewer to 16 fewer)		
	50%		320 fewer per 1000 (from 195 fewer to 390 fewer)		
0/52 (0%)	4/60 (6.7%)	RR 0.13 (0.01–2.32)	58 fewer per 1000 (from 66 fewer to 88 more)	⊕⊕OO LOW	CRITICAL
	2%		17 fewer per 1000 (from 20 fewer to 26 more)		
	50%		435 fewer per 1000 (from 495 fewer to 660 more)		
71/693 (10.2%)	84/618 (13.6%)	RR 0.74 (0.55–1)	35 fewer per 1000 (from 61 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
	2%		5 fewer per 1000 (from 9 fewer to 0 more)		
	50%		130 fewer per 1000 (from 225 fewer to 0 more)		
6/11 (54.5%)	38/25 (152%)	RR 0.36 (0.15–0.85)	973 fewer per 1000 (from 228 fewer to 1292 fewer)	⊕⊕⊕O MODERATE	CRITICAL
	10%		64 fewer per 1000 (from 15 fewer to 85 fewer)		
	50%		320 fewer per 1000 (from 75 fewer to 425 fewer)		

GRADE profile table 5: Efficacy of INH vs placebo in persons who are TST negative

Bibliography: Fitzgerald et al. 2001; Gordin et al. 1997; Hawken et al. 1997; Mwinga et al. 1998; Pape et al. 1993; Rivero et al. 2003; Whalen et al.1997– anergy

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Active TB incidence (probable, possible, confirmed) (follow up 1-3 years; clinical examination, chest X-ray, sputum for AFB)						
7	Randomized trials	No serious limitations	No serious inconsistency[1]	No serious indirectness	No serious imprecision	None
Confirmed TB (follow up 1-3 years; culture-proven)						
3	Randomized trials	No serious limitations	Serious[2]	No serious indirectness	No serious imprecision	None
Mortality (any cause) (follow up 1-3 years; review of hospital records)						
7	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None
HIV disease progression (follow up 1-3 years; clinical and immunological criteria)						
2	Randomized trials	No serious limitations	Serious[3]	No serious indirectness	No serious imprecision	None

[1] Fitzgerald et al. and Hawken et al. showed an opposite direction of the effect
[2] Different direction of the effect across studies
[3] Opposite direction of the effect

Summary of findings					
No. of patients		Effect		Quality	Importance
INH prophylaxis	Control	Relative risk (95% CI)	Absolute		
49/1297 (3.8%)	54/1193 (4.5%)	RR 0.86 (0.59–1.26)	6 fewer per 1000 (from 19 fewer to 12 more)	⊕⊕⊕⊕ HIGH	CRITICAL
	2%		3 fewer per 1000 (from 8 fewer to 5 more)		
	50%		70 fewer per 1000 (from 205 fewer to 130 more)		
12/521 (2.3%)	15/500 (3%)	RR 0.76 (0.36–1.61)	7 fewer per 1000 (from 19 fewer to 18 more)	⊕⊕⊕O MODERATE	CRITICAL
	2%		5 fewer per 1000 (from 13 fewer to 12 more)		
	50%		120 fewer per 1000 (from 320 fewer to 305 more)		
328/1297 (25.3%)	298/1193 (25%)	RR 1.02 (0.9–1.16)	5 more per 1000 (from 25 fewer to 40 more)	⊕⊕⊕⊕ HIGH	CRITICAL
	2%		0 more per 1000 (from 2 fewer to 3 more)		
	50%		10 more per 1000 (from 50 fewer to 80 more)		
35/146 (24%)	32/146 (21.9%)	RR 1.10 (0.72–1.69)	22 more per 1000 (from 61 fewer to 151 more)	⊕⊕⊕O MODERATE	CRITICAL
	10%		10 more per 1000 (from 28 fewer to 69 more)		
	50%		50 more per 1000 (from 140 fewer to 345 more)		

GRADE profile table 6: Efficacy of INH vs placebo in persons with unknown TST status

Bibliography: Mwinga et al. 1998; Hawken et al. 1997

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Active TB incidence (probable, possible, confirmed) (follow up 1-3 years; clinical examination, chest X-ray, sputum for AFB)						
2	Randomized trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None
Confirmed TB (follow up 1-3 years; culture-proven)						
2	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None
Mortality (any cause) (follow up 1-3 years; review of hospital records)						
2	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None
HIV disease progression (follow up 1-3 years; clinical and immunological criteria)						
0	No evidence available					None

[1] Opposite direction of the effect

Summary of findings					
No. of patients		Effect		Quality	Importance
INH prophylaxis	Control	Relative risk (95% CI)	Absolute		
18/162 (11.1%)	23/173 (13.3%)	RR 0.86 (0.48–1.52)	19 fewer per 1000 (from 69 fewer to 69 more)	⊕⊕⊕O MODERATE	CRITICAL
	2%		3 fewer per 1000 (from 10 fewer to 10 more)		
	50%		70 fewer per 1000 (from 260 fewer to 260 more)		
22/464 (4.7%)	28/466 (6%)	RR 0.79 (0.46–1.36)	13 fewer per 1000 (from 32 fewer to 22 more)	⊕⊕⊕⊕ HIGH	CRITICAL
	2%		4 fewer per 1000 (from 11 fewer to 7 more)		
	50%		105 fewer per 1000 (from 270 fewer to 180 more)		
28/162 (17.3%)	37/173 (21.4%)	RR 0.81 (0.52–1.27)	41 fewer per 1000 (from 103 fewer to 58 more)	⊕⊕⊕⊕ HIGH	CRITICAL
	2%		4 fewer per 1000 (from 10 fewer to 5 more)		
	50%		95 fewer per 1000 (from 240 fewer to 135 more)		
0/0 (0%)	0/0 (0%)	RR 0 (0–0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
	0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

GRADE profile table 7: Duration of IPT in adults – INH 6 months vs 36 months

Bibliography: Martinson et al.2009; Samandari et al. 2009

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Active TB incidence (probable, possible, confirmed) (follow up mean 36 months; clinical assessment, chest X-ray, sputum for AFB)						
2	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2, 3, 4]	No serious imprecision	None
Confirmed TB (follow up mean 36 months; culture-proven)						
1	Randomized trials	No serious limitations	No serious inconsistency	Serious	No serious imprecision	None
Mortality (any cause) (follow up 36 months; review of hospital records and patients' files)						
2	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2, 3, 4]	No serious imprecision	None
HIV disease progression						
0[5]	No evidence available					None
Adverse drug reactions leading to treatment interruption (follow up 36 months; laboratory monitoring and clinical assessment)						
2	Randomized trials	No serious limitations	Serious[6]	No serious indirectness	No serious imprecision	None

[1] The Soweto trial was not a head-to-head comparison but a four-arm study designed to compare the efficacy of different regimens as well
[2] The Soweto trial considered TST-positive patients while the BOTUSA trial enrolled TST-positive and -negative patients
[3] Mean CD4 count at baseline was >500 cells/mm^3 for the Soweto trial and around 200 cells/mm^3 for the BOTUSA trial
[4] The Soweto trial enrolled patients not eligible for ART, while in the Botusa trial about 40% of the patients had started ART
[5] Subanaylsis on this outcome is expected to be performed soon.
[6] The number of the affected is quite different between studies.

Summary of findings					
No. of patients		Effect		Quality	Importance
Continuous INH prophylaxis	**6 months INH prophylaxis**	Relative risk (95% CI)	Absolute		
20/997 (2%)	46/1150 (4%)	RR 0.50 (0.29–0.84)	20 fewer per 1000 (from 6 fewer to 28 fewer)	⊕⊕⊕O MODERATE	CRITICAL
	2%		10 fewer per 1000 (from 3 fewer to 14 fewer)		
	50%		250 fewer per 1000 (from 80 fewer to 355 fewer)		
14/997 (1.4%)	33/1150 (2.9%)	RR 0.48 (0.26–0.9)	15 fewer per 1000 (from 3 fewer to 21 fewer)	⊕⊕⊕O MODERATE	CRITICAL
	2%		10 fewer per 1000 (from 2 fewer to 15 fewer)		
	50%		260 fewer per 1000 (from 50 fewer to 370 fewer)		
15/997 (1.5%)	40/1150 (3.5%)	RR 0.43 (0.24–0.78)	20 fewer per 1000 (from 8 fewer to 26 fewer)	⊕⊕⊕O MODERATE	CRITICAL
	10%		57 fewer per 1000 (from 22 fewer to 76 fewer)		
	50%		285 fewer per 1000 (from 110 fewer to 380 fewer)		
0/0 (0%)	0/0 (0%)	RR 0 (0–0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
	0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
70/983 (7.1%)	12/846 (1.4%)	RR 5.02 (2.74–9.198)	57 more per 1000 (from 25 more to 116 more)	⊕⊕⊕O MODERATE	CRITICAL
	1%		40 more per 1000 (from 17 more to 82 more)		

GRADE profile table 8: Duration of IPT in adults INH 6 months vs 12 months in those with any TST status

Bibliography: Pape et al. 1993; Whalen et al. 1997; Hawken et al. 1997; Mwinga et al. 1998; Fitzgerald et al. 2001; Gordin et al. 1997; Rivero et al. 2003; Whalen et al.1997 – anergy

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Active TB--possible, probable, confirmed (follow up 1–3 years; clinical assessment, chest X-ray, sputum for AFB)						
8	Randomized trials	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None
Confirmed TB (follow up 1–3 years; culture-proven)						
0	No evidence available					None
Mortality (any cause) (follow up 1–3 years; review of hospital records and patients' files)						
2	Randomized trials	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None
HIV disease progression						
0	No evidence available					None
Adverse drug reactions leading to treatment interruption (follow up 1–3 years; laboratory monitoring and clinical assessment)						
12	Randomized trials	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None

[1] Not estimable due to the lack of events in the 12 months' group.

Summary of findings					
No. of patients		Effect		Quality	Importance
6 months of INH prophylaxis	12 months of INH prophylaxis	Relative risk (95% CI)	Absolute		
57/1806 (3.2%)	10/184 (5.4%)	RR 0.58 (0.3–1.12)	23 fewer per 1000 (from 38 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
	2%		8 fewer per 1000 (from 14 fewer to 2 more)		
	50%		210 fewer per 1000 (from 350 fewer to 60 more)		
0/0 (0%)	0/0 (0%)	RR 0 (0–0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
	0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
	0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
375/1806 (20.8%)	24/184 (13%)	RR 1.59 (1.085–2.34)	77 more per 1000 (from 11 more to 175 more)	⊕⊕OO LOW	CRITICAL
	10%		59 more per 1000 (from 9 more to 134 more)		
	50%		295 more per 1000 (from 43 more to 670 more)		
0/0 (0%)	0/0 (0%)	RR 0 (0–0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
	0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
56/1968 (2.8%)	0/58 (0%)	RR 0 (0–0)[1]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	CRITICAL
	0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

GRADE profile table 9: Efficacy in children – INH 6 months vs placebo

Bibliography: Zar et al. 2007; Madhi et al. 2008

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Active TB (follow up 5.7–9 months; clinical algorithm criteria, chest X-ray, bacteriological isolates from any site)						
2	Randomized trials	No serious limitations	Serious[1]	No serious indirectness[2]	No serious imprecision	None
Confirmed TB (follow up 5.7–9 months; culture-proven)						
1	Randomized trials	No serious limitations	Serious[3]	No serious indirectness	Serious[4]	None
Mortality (all causes) (follow up 5.7–9 months; review of hospital records and patients' files)						
2	Randomized trials	No serious limitations	Serious[1]	No serious indirectness[2]	No serious imprecision	None
Adverse reaction (grade 3 or 4 toxicity) (follow up 5.7–9 months; clinical and laboratory monitoring)						
2	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness[5]	No serious imprecision	None
HIV disease progression						
0						None

[1] Opposite direction of the effect.
[2] P1041 represents an optimal HIV care setting, with good facilities to rule out active TB: children were younger, healthier and presented in a less advanced stage of disease; the study by Zar et al. represents the most common condition of rural areas with later diagnosis of TB, fewer resources, and children presenting with more advanced disease and challenging TB diagnosis.
[3] One trial available.
[4] Wide confidence intervals.
[5] Rough data are missing for P1041 (but no significant difference was reported between the two groups).

Summary of findings					
No. of patients		Effect		Quality	Importance
INH prophylaxis (6 months)	**Placebo**	Relative risk (95% CI)	Absolute		
44/358 (12.3%)	45/357 (12.6%)	RR 0.97 (0.6609–1.4384)	4 fewer per 1000 (from 43 fewer to 55 more)	⊕⊕⊕O MODERATE	CRITICAL
	5%		1 fewer per 1000 (from 17 fewer to 22 more)		
3/226 (1.3%)	3/226 (1.3%)	RR 1.5 (0.25–8.89)	7 more per 1000 (from 10 fewer to 105 more)	⊕⊕OO LOW	CRITICAL
	0.9%		4 more per 1000 (from 7 fewer to 71 more)		
26/358 (7.3%)	31/357 (8.7%)	RR 0.84 (0.51–1.37)	14 fewer per 1000 (from 43 fewer to 32 more)	⊕⊕⊕O MODERATE	CRITICAL
	10%		16 fewer per 1000 (from 49 fewer to 37 more)		
5/132 (3.8%)	8/131 (6.1%)	RR 0.62 (0.21–1.85)	23 fewer per 1000 (from 48 fewer to 52 more)	⊕⊕⊕⊕ HIGH	CRITICAL
	0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
0/0 (0%)	0/0 (0%)	RR 0 (0–0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
	0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

GRADE profile table 10: Drug resistance and use of preventive therapy

Bibliography: Hawken 1997; Johnson et al. 2001; Pape et al. 1993; Rivero et al. 2003; Saenghirunvatta 1996; Zar et al. 2007; le Roux et al. 2009; Mwinga et al. 1998; Halsey et al. 1998; Gordin et al. 2000

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Mono-resistance to INH vs placebo (IPT intervention vs placebo)						
7	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None
Mono-resistance to INH vs rifampicin (IPT intervention vs rifampicin as control)						
3	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None

[1] Incomplete accounting of patients and outcomes
[2] Small number of cases and patients
[3] Small number of patients

GRADE profile table 11: Secondary prophylaxis

Bibliography: Perriens et al. 1995; Haller et al. 1999; Fitzgerald et al. 2000; Churchyard et al. 2003

Quality assessment						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
TB recurrence (observational) (follow up 0.91 vs 0.41 patient-years; isoniazid vs co-trimoxazole)						
1	Observational study	Serious	No serious inconsistency	Serious	No serious imprecision	Strong association
TB recurrence (randomized)						
3	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness[1]	Serious[2]	None

[1] The study by Perriens et al. provided INH and rifampicin for six months instead of INH alone
[2] Small numbers in study

Summary of findings					
No. of patients		Effect		Quality	Importance
Anti-TB medications	No medications	Relative risk (95% CI)	Absolute		
11/1255(0.9%)	5/1069 (0.5%)	RR 1.87 (0.65–5.38)	4 more per 1000 (from 2 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
3/1469 (0.2%)	1/1469 (0.1%)	RR 2 (0.18–22.03)	1 more per 1000 (from 1 fewer to 14 fewer)	⊕OOO VERY LOW	LESS CRITICAL

Summary of findings					
No. of patients		Effect		Quality	Importance
Secondary treatment of LTBI	Control	Relative risk (95% CI)	Absolute		
28/338 (8.3%)	23/221 (10.4%)	RR 0.45 (0.26–0.78)	57 fewer per 1000 (from 23 fewer to 77 fewer)	⊕OOO VERY LOW	CRITICAL
7/275 (2.5%)	31/286 (10.8%)	RR 0.23 (0.11–0.52)	83 fewer per 1000 (from 52 fewer to 96 fewer)	⊕⊕⊕O MODERATE	LESS CRITICAL

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Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings

Tuberculosis (TB) is responsible for more than a quarter of deaths in people living with HIV. Isoniazid Preventive Therapy (IPT) and Intensified tuberculosis Case Finding (ICF) are key public health interventions that significantly reduce the morbidity and mortality from TB in people living with HIV. IPT and ICF should be part of a TB prevention package along with infection control for TB and the provision of ART.

The objective of these guidelines is to provide guidance to national AIDS and tuberculosis programmes and those providing HIV services to accelerate the nationwide implementation of IPT and ICF. They include evidence-based recommendations for adults, children and infants living with HIV, address implementation issues and identify key research gaps in order to scale up TB prevention, diagnosis and treatment as a core component of HIV prevention, treatment and care. They are aimed at policy-makers and health programme managers, governments, nongovernmental organizations, donors, patient support groups working in the field of HIV/AIDS and TB and health-care workers providing care for people living with HIV.

World Health Organization

9789241500708

What I need to know about

Hepatitis B

U.S. Department of Health and Human Services
NATIONAL INSTITUTES OF HEALTH

NIDDK | NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
National Digestive Diseases Information Clearinghouse

What I need to know about Hepatitis B

U.S. Department of Health and Human Services
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National Digestive Diseases Information Clearinghouse

Contents

What is hepatitis B?

Hepatitis B is a liver disease. **Hepatitis*** means **inflammation** of the liver. Inflammation is the painful, red swelling that results when tissues of the body become injured or infected. Inflammation can cause organs to not work properly.

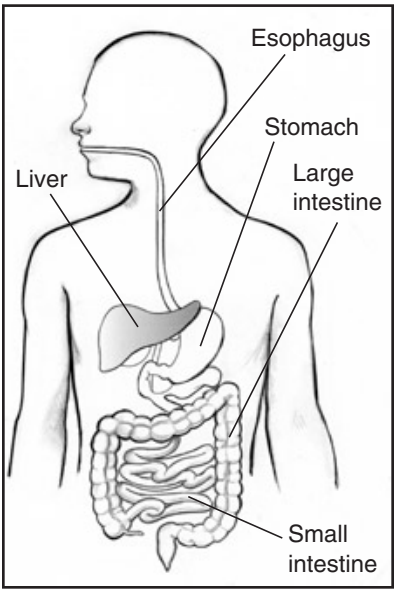
What is the liver?

The liver is an organ that does many important things.

The liver

- removes harmful chemicals from your blood
- fights infection
- helps digest food
- stores nutrients and vitamins
- stores energy

You cannot live without a liver.



Hepatitis B is a liver disease.

*See page 13 for tips on how to say the words in **bold** type.

What causes hepatitis B?

The hepatitis B **virus** causes hepatitis B. Viruses are germs that can cause sickness. For example, the flu is caused by a virus. People can pass viruses to each other.

Who gets hepatitis B?

Anyone can get hepatitis B, but some people are at higher risk, including

- people who were born to a mother with hepatitis B
- people who live with someone who has hepatitis B
- people who have lived in parts of the world where hepatitis B is common
- people who are exposed to blood or body fluids at work
- people on hemodialysis
- people who have had more than one sex partner in the last 6 months or have a history of sexually transmitted disease
- injection drug users
- men who have sex with men

How could I get hepatitis B?

You could get hepatitis B through contact with an infected person's blood, semen, or other body fluid.

You could get hepatitis B from

- being born to a mother with hepatitis B
- having sex with an infected person
- being tattooed or pierced with unsterilized tools that were used on an infected person
- getting an accidental needle stick with a needle that was used on an infected person
- using an infected person's razor or toothbrush
- sharing drug needles with an infected person

You could get hepatitis B from having sex with an infected person.

You cannot get hepatitis B from

- shaking hands with an infected person
- hugging an infected person
- sitting next to an infected person

What are the symptoms of hepatitis B?

Hepatitis B usually has no symptoms. Adults and children ages 5 and older sometimes have one or more of the following symptoms:

- yellowish eyes and skin, called **jaundice**
- a longer than usual amount of time for bleeding to stop
- swollen stomach or ankles
- easy bruising
- tiredness
- upset stomach
- fever
- loss of appetite
- diarrhea
- light-colored stools
- dark yellow urine

What is chronic hepatitis B?

Hepatitis B is **chronic** when the body can't get rid of the hepatitis B virus. Children, especially infants, are more likely to get chronic hepatitis B, which usually has no symptoms until signs of liver damage appear. Without treatment, chronic hepatitis B can cause scarring of the liver, called **cirrhosis**; liver cancer; and liver failure.

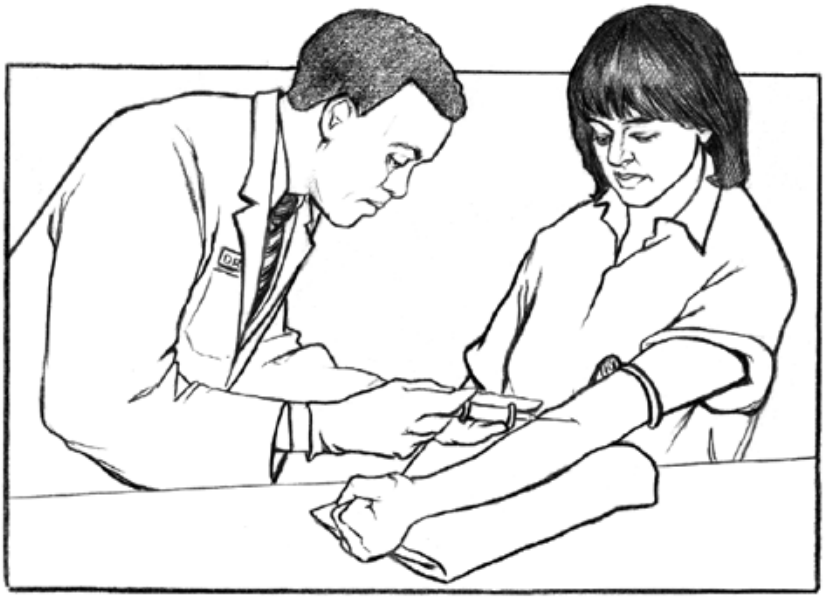
Symptoms of cirrhosis include

- yellowish eyes and skin, called jaundice
- a longer than usual amount of time for bleeding to stop
- swollen stomach or ankles
- tiredness
- nausea
- weakness
- loss of appetite
- weight loss
- spiderlike blood vessels, called spider **angiomas**, that develop on the skin

How is hepatitis B diagnosed?

Hepatitis B is diagnosed through blood tests, which can also show if you have chronic hepatitis B or another type of hepatitis.

Your doctor may suggest getting a liver **biopsy** if chronic hepatitis B is suspected. A liver biopsy is a test for liver damage. The doctor uses a needle to remove a tiny piece of liver, which is then looked at with a microscope.



Blood is drawn for hepatitis B testing.

How is hepatitis B treated?

Hepatitis B usually is not treated unless it becomes chronic.

Chronic hepatitis B is treated with drugs that slow or stop the virus from damaging the liver. The length of treatment varies. Your doctor will help you decide which drug or drug combination is likely to work for you and will closely watch your symptoms to make sure treatment is working.

Drugs given by shots include

- **interferon**
- **peginterferon**

Drugs taken by mouth include

- **lamivudine**
- **telbivudine**
- **adefovir**
- **entecavir**

Liver Transplantation

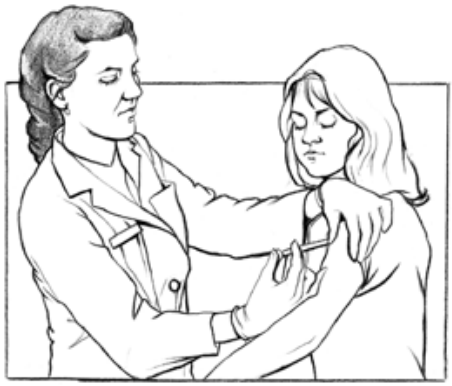
A liver transplant may be necessary if chronic hepatitis B causes liver failure. Liver transplantation surgery replaces a failed liver with a healthy one from a donor. Medicines taken after surgery can prevent hepatitis B from coming back.

How can I avoid getting hepatitis B?

You can avoid getting hepatitis B by getting the hepatitis B **vaccine**.

Vaccines are medicines that keep you from getting sick. Vaccines teach your body to attack specific germs. The hepatitis B vaccine teaches your body to attack the hepatitis B virus.

Adults at higher risk of getting hepatitis B and all children should get the vaccine. The hepatitis B vaccine is given through three shots over a period of several months. There is no minimum age for vaccination. The second shot should be given at least 1 month after the first, and the last shot should be given at least 2 months



The hepatitis B vaccine protects you from infection.

after the second shot but no sooner than 4 months after the first. The hepatitis B vaccine is safe for pregnant women.

You need all three shots to be fully protected. If you are traveling to a country where hepatitis B is common, try to get all the shots before you go. If you don't have time to get all the shots before you go, get as many as you can. One shot may provide some protection against the virus.

You can also protect yourself and others from hepatitis B if you

- use a condom during sex
- do not share drug needles
- wear gloves if you have to touch another person's blood
- do not borrow another person's toothbrush, razor, or anything else that could have blood on it
- make sure any tattoos or body piercings you get are done with sterile tools
- do not donate blood or blood products if you have hepatitis B

Wear gloves if you have to touch another person's blood.

What should I do if I think I have been exposed to the hepatitis B virus?

See your doctor right away if you think you have been exposed to the hepatitis B virus. The first shot of the hepatitis B vaccine taken with a medicine called hepatitis B immune globulin may prevent you from getting sick.

If you are at higher risk of hepatitis B, get tested. Many people do not know they are infected. Early diagnosis and treatment can help prevent liver damage.

Points to Remember

- Hepatitis B is a liver disease caused by the hepatitis B virus.
- Anyone can get hepatitis B, but some people are at higher risk.
- You could get hepatitis B through contact with an infected person's blood, semen, or other body fluid.
- Hepatitis B usually has no symptoms.
- Adults and children ages 5 and older sometimes have jaundice or other symptoms.

- Hepatitis B usually is not treated unless it becomes chronic.
- Hepatitis B is chronic when the body can't get rid of the hepatitis B virus.
- Children, especially infants, are more likely to develop chronic hepatitis B.
- Chronic hepatitis B is treated with drugs that slow or stop the virus from damaging the liver.
- You can protect yourself from getting hepatitis B by getting the hepatitis B vaccine.
- See your doctor right away if you think you've been exposed to the hepatitis B virus.
- If you are at higher risk of hepatitis B, get tested. Many people do not know they are infected. Early diagnosis and treatment can help prevent liver damage.

Hope through Research

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research into many digestive disorders, including hepatitis B. NIDDK scientists are researching better strategies for using antiviral medicines to treat hepatitis B.

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research. For information about current studies, visit *www.ClinicalTrials.gov*.

Pronunciation Guide

adefovir (ad-DEF-oh-vihr)

angiomas (an-jee-OH-muhs)

biopsy (BY-op-see)

chronic (KRON-ik)

cirrhosis (sur-ROH-siss)

entecavir (INT-ih-CAH-vihr)

hepatitis (HEP-uh-TY-tiss)

inflammation (IN-fluh-MAY-shuhn)

interferon (IN-tur-FIHR-on)

jaundice (JAWN-diss)

lamivudine (luh-MIH-vyoo-deen)

peginterferon (PEG-IN-tur-FIHR-on)

telbivudine (tel-BIH-vyoo-deen)

vaccine (vak-SEEN)

virus (VY-ruhss)

For More Information

American Liver Foundation
75 Maiden Lane, Suite 603
New York, NY 10038–4810
Phone: 1–800–GO–LIVER (1–800–465–4837)
or 212–668–1000
Fax: 212–483–8179
Email: info@liverfoundation.org
Internet: www.liverfoundation.org

Hepatitis B Foundation
3805 Old Easton Road
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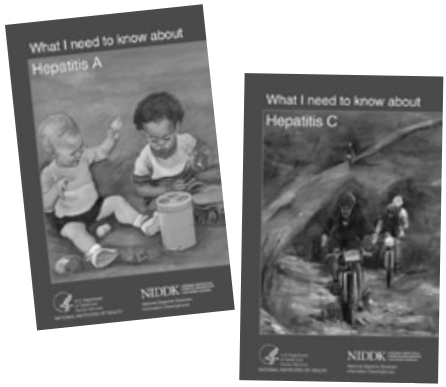
Phone: 215–489–4900
Fax: 215–489–4913
Email: info@hepb.org
Internet: www.hepb.org

Hepatitis Foundation International
504 Blick Drive
Silver Spring, MD 20904–2901
Phone: 1–800–891–0707 or 301–622–4200
Fax: 301–622–4702
Email: hfi@comcast.net
Internet: www.hepfi.org

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333
Phone: 1–800–311–3435 or 404–639–3534
Email: cdcinfo@cdc.gov
Internet: www.cdc.gov/nchhstp

Other types of hepatitis exist. The National Digestive Diseases Information Clearinghouse (NDDIC) also has booklets about hepatitis A and hepatitis C:

- *What I need to know about Hepatitis A*
- *What I need to know about Hepatitis C*



You can get a free copy of each booklet by calling 1–800–891–5389, by going online to *www.catalog.niddk.nih.gov*, or by writing to

NDDIC
2 Information Way
Bethesda, MD 20892–3570

Hepatitis information for health professionals is also available.

Acknowledgments

Publications produced by the Clearinghouse are carefully reviewed by both NIDDK scientists and outside experts. The individuals listed here provided editorial guidance or facilitated field-testing for the original version of this publication. The NDDIC would like to thank these individuals for their contribution.

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Email: nddic@info.niddk.nih.gov
Internet: www.digestive.niddk.nih.gov

The National Digestive Diseases Information Clearinghouse (NDDIC) is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK is part of the National Institutes of Health of the U.S. Department of Health and Human Services. Established in 1980, the Clearinghouse provides information about digestive diseases to people with digestive disorders and to their families, health care professionals, and the public. The NDDIC answers inquiries, develops and distributes publications, and works closely with professional and patient organizations and Government agencies to coordinate resources about digestive diseases.

This booklet is also available at *www.digestive.niddk.nih.gov*.

This publication may contain information about medications. When prepared, this publication included the most current information available. For updates or for questions about any medications, contact the U.S. Food and Drug Administration toll-free at 1–888–INFO–FDA (1–888–463–6332) or visit *www.fda.gov*. Consult your doctor for more information.

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NIH Publication No. 09–4228
April 2009