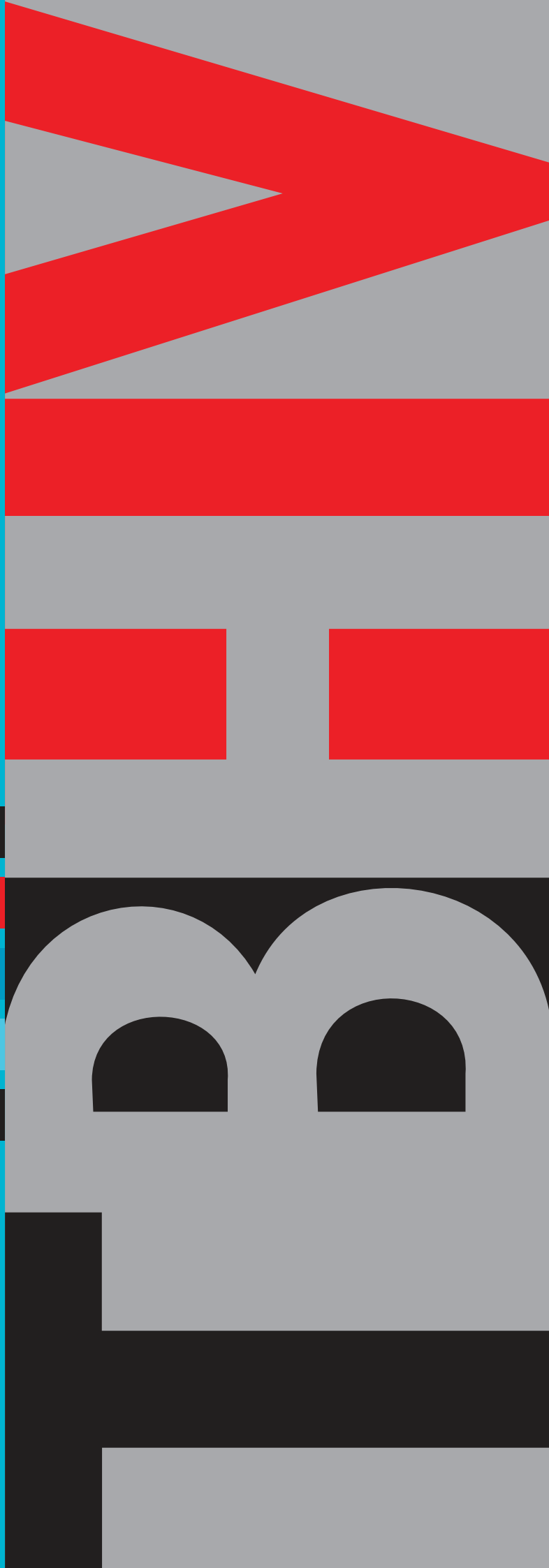
WHO policy on collaborative TB/HIV activities

Guidelines for national programmes and other stakeholders

Annexes
for webposting and CD-Rom distribution with the policy guidelines



World Health Organization

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Contents: Annexes for webposting and CD-ROM distribution with the policy guidelines

1.HIV infections. 2.Acquired immunodeficiency syndrome - prevention and control. 3.AIDS-related opportunistic infections - prevention and control. 4.Tuberculosis, Pulmonary - prevention and control. 5.National health programs. 6.Health policy. 7.Guidelines. I.World Health Organization.

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These guidelines were developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the *WHO handbook for guideline development* (version March 2010).

Designed by Creative Lynx, Geneva, Switzerland

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Summary of declaration of interests

All members of the Policy Updating Group were asked to complete a World Health Organization (WHO) *Declaration of interests for WHO consultants* form. Five members of the group declared a conflict of interest. Constance Benson declared consulting, scientific and technical advisory work on antiretroviral therapy new drug development with Merck, GlaxoSmithKline and ViiV for less than US$ 5000 each. Pedro Cahn declared ongoing research support and consulting work with Abbott for an amount of US$ 3000. He declared receiving US$ 2000 from Bristol-Myers Squibb and US$ 2000 from Tibotec for serving on a speakers' bureau. He also declared scientific advisory work for Merck, Pfizer, GlaxoSmithKline and Avexa for an amount of US$ 2000 each. Mark Harrington declared giving testimony to the Institute of Medicine of the United States National Academies in panels on multidrug-resistant TB in 2008 and 2009. Charles Holmes declared employment by Gilead up to January 2008 in the clinical research unit focusing on phase I studies of experimental antiretroviral drugs. He declared no financial or other interest in Gilead. Salim S. Abdool Karim declared receiving US$ 2500 from Merck to attend the advisory panel meeting on microbicides in March 2011.

The declared conflicts of interest were discussed within the WHO Steering Group and with the Policy Updating Group before deliberations on the policy document, and it was concluded that these conflicts would not prohibit any of the members from participating in the process. Declarations of interest were collected from all non-WHO reviewers. Four peer reviewers declared potential conflicts of interest. Helen Ayles declared an ongoing research grant for her research unit with Delft Diagnostic Systems of € 100 000 to develop a computer-aided diagnostic for reading digital chest X-rays as well as having received a digital chest X-ray unit for an amount of US$ 250 000. François Boillot declared being the owner, director of and employed by a consulting company providing services in international health including in TB/HIV issues. Susan Swindells declared consulting services (advisory board) with Pfizer in 2008 (US$ 1800) and 2009 (US$ 1750), with Merck in 2009 (US$ 3500), with Tibotec in 2009 (US$ 1500) and with Abbott Molecular in 2010 (US$ 1000). She also declared previous research support to her institution from Bristol Myers Squibb that ended in 2010 (US$ 14929), from Pfizer that ended in 2011 (US$ 28125) and ongoing research support from GlaxoSmithKline for an amount of US$ 104034 and US$ 60676. Jay K. Varma declared non-monetary support (supplies and equipment) in 2010 valued at approximately US$ 10 000 from Cellestis to the government research unit of China and collaborators in Inner Mongolia to examine the prevalence of TB in health-care workers in collaboration with the United States Centers for Disease Control and Prevention. The WHO Steering Group discussed these declarations and concluded that they would not exclude the reviewers from the process. All declarations of conflict of interests are retained on electronic file by the WHO Stop TB Department.

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WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders is based on the interim policy on collaborative TB/HIV activities published in 2004 by the World Health Organization (WHO) and written by Haileyesus Getahun, Jeroen van Gorkom, Anthony Harries, Mark Harington, Paul Nunn, Jos Perriens, Alasdair Reid and Marco Vitoria on behalf of the TB/HIV policy writing committee for the Global TB/HIV Working Group of the Stop TB Partnership. This updated policy was written by Delphine Sculier and Haileyesus Getahun (Stop TB Department, WHO) in collaboration with the WHO Steering Group.

WHO Steering Group

Rachel Baggaley (HIV/AIDS Department), Haileyesus Getahun (Stop TB Department), Reuben Granich (HIV/AIDS Department), Christian Gunneberg (Stop TB Department), Craig McClure (HIV/AIDS Department), Eyerusalem Negussie (HIV/AIDS Department), Delphine Sculier (Stop TB Department), Marco Vitoria (HIV/AIDS Department).

WHO consultants for systematic and GRADE reviews

Martina Penazzato (Italy), Amitabh Suthar (USA), Helena Legido-Quigley (UK).

Policy updating group

Yibeltal Assefa (Federal HIV/AIDS Prevention and Control Office, Ethiopia), Abdool Karim S. Abdool Salim (Centre for the AIDS Programme of Research in South Africa, South Africa), Rifat Atun (Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund), Switzerland), Constance Benson (University of California, San Diego, USA), Amy Bloom (United States Agency for International Development (USAID), USA), Pedro Cahn (Fundación Huésped, Argentina), Rolando Cedillos (Proyecto Regional VIH SIDA para Centroamérica, El Salvador), Richard E. Chaisson (Johns Hopkins Bloomberg School of Public Health Center for TB Research, USA), Jeremiah Chakaya (Kenya Medical Research Institute (KEMRI), Kenya), Lucy Chesire (Advocacy to Control TB Internationally, Kenya), Mean Chhi Vun (National Center for HIV/AIDS, Dermatology and Sexually Transmitted Diseases, Cambodia), Gavin Churchyard (Aurum Institute for Health Research, South Africa), William Coggin (Office of the US Global AIDS Coordinator (OGAC), USA), Riitta Dlodlo (International Union Against Tuberculosis and Lung Disease (The Union), Zimbabwe), Ade Fakoya, (The Global Fund, Switzerland), Peter Godfrey-Fausset (London School of Hygiene & Tropical Medicine, UK), Anthony Harries (The Union, UK), Mark Harrington (Treatment Action Group, USA), Diane Havlir (University of California, San Francisco, USA), Charles Holmes (OGAC, USA), Nina Kerimi (United Nations Office on Drugs and Crime, Kazakhstan), Robert Makombe (United States Centers for Disease Control and Prevention (CDC), Botswana), Bess Miller (Global AIDS Program, USA), Ya-Diul Mukadi (USAID, USA), Jintanta Ngamvithayapong-Yanai (Research Institute of Tuberculosis, Japan), Alasdair Reid (Joint United Nations Programme on HIV/AIDS, Switzerland), BB Rewari (National AIDS Control Organization, India), Ashurova Rukshona (National Center for Prevention and Control of AIDS, Tajikistan), Holger Schünemann (McMaster University Health Sciences Centre, Canada), Lakhbir Singh Chauhan (Central TB Division, Ministry of Health and Family Welfare, India), Joseph Sitienei (Division of Leprosy, TB and Lung Diseases, Kenya), Alena Skrahina (Republic Scientific and Practical Center of Pulmonology and Tuberculosis, Belarus), John Stover (Future Institutes, USA), Jeroen van Gorkom (KNCV Tuberculosis Foundation, Netherlands).

External peer reviewers

Helen Ayles (ZAMBART Project, Zambia), François-Xavier Blanc (Agence nationale de recherche sur le sida et les hépatites virales, France), François Boillot (Alter-Santé Internationale et Développement, France), John T. Brooks (CDC, USA), Kevin Cain (KEMRI/CDC, Kenya), Wafaa El-Sadr (Columbia University, New York, USA), Eric Goemare (Médecins Sans Frontières (MSF), South Africa), Yared Kebede Haile (KNCV Tuberculosis Foundation, Netherlands), Steve D. Lawn (University of Cape Town, South Africa), Gary Maartens (University of Cape Town, South Africa), Barbara J. Marston (CDC, USA), Elizabeth Marum (CDC, Zambia), Max Meis (KNCV Tuberculosis Foundation, Netherlands), Sue Perez (free lance consultant, USA), Eric S. Pevzner (CDC, USA), Yogan Pillay (Strategic Health Programme, Department of Health, South Africa), Peter Saranchuk (MSF, South Africa), Kenly Sikwese (Global Network of People Living with HIV/AIDS, Zambia), Susan Swindells (University of Nebraska Medical Center, USA), Javid Syed (Treatment Action Group, USA), Nonna Turusbekova (KNCV Tuberculosis Foundation, Netherlands), Marieke van der Werf (KNCV Tuberculosis Foundation, Netherlands), Eric van Praag (Family Health International, United Republic of Tanzania), Jay K. Varma (CDC, China), Lynne Wilkinson (MSF, South Africa), Rony Zachariah (MSF, Belgium).

WHO headquarters and regional offices

Leopold Blanc (Stop TB Department), Puneet Dewan (Regional Office for South-East Asia), Gottfried Hirnschall (HIV/AIDS Department), Khurshid Hyder (Regional Office for South-East Asia), Rafael Lopez Olarte (Regional Office for the Americas), Frank Lule (Regional Office for Africa), Mario Raviglione (Stop TB Department), Ying-Ru Lo (HIV/AIDS Department), Caoimhe Smyth (HIV/AIDS Department).

Editor

Karin Ciceri

Coordination

Delphine Sculier and Haileyesus Getahun (Stop TB Department, WHO).

Contents

Abbreviations

AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CI	confidence interval
CPT	co-trimoxazole preventive therapy
GRADE	grading of recommendations assessment, development and evaluation
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HR	hazard ratio
IPT	isoniazid preventive therapy
IRR	incidence rate ratio
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
PICO	population, intervention, comparison, outcome
RCT	randomized controlled trial
RR	risk ratio
SD	standard deviation
TB	tuberculosis
TB/HIV	The intersecting epidemics of TB and HIV
TST	tuberculin skin test
VCT	voluntary counselling and testing
WHO	World Health Organization

Annex 1

Earlier initiation of antiretroviral therapy prevents active tuberculosis in people living with HIV – summary of findings and evaluation of the quality of the evidence

PICO question: Can earlier initiation of antiretroviral therapy (ART) at higher CD4 counts (>350 cells/mm^3) be used to prevent active tuberculosis in people living with HIV? Should antiretroviral therapy be used to prevent active tuberculosis?

Population: adults and adolescents living with HIV

Intervention: ART at CD4 counts >350 cells/mm^3

Comparison: no ART or ART deferred until CD4 counts ≤350 cells/mm^3

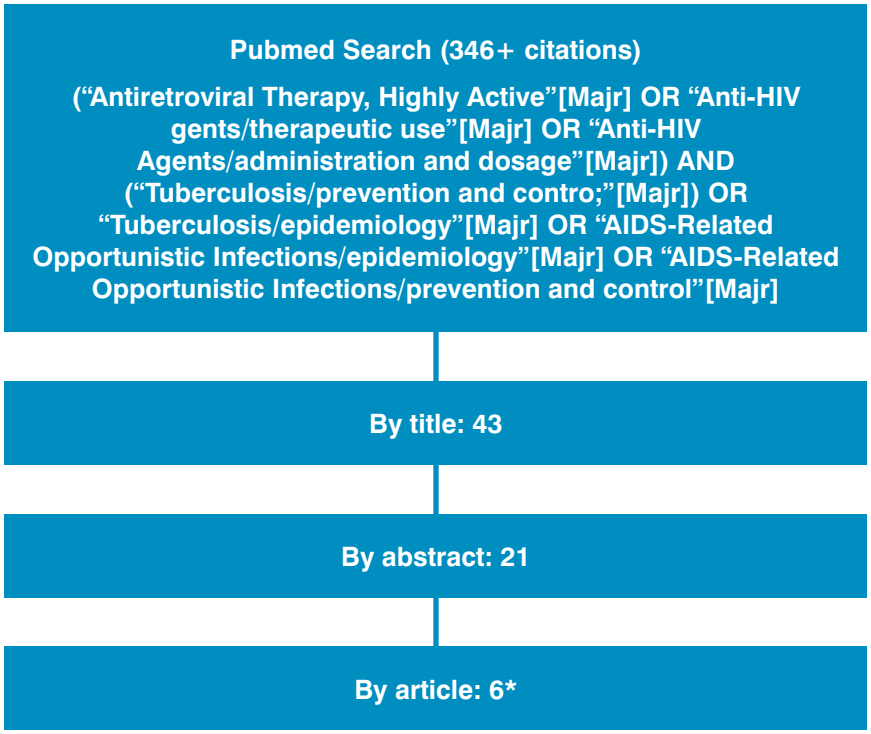
Outcomes: TB incidence rate

1. Outcomes of interest

Outcomes	Relative importance (rank 1 → 9 most critical)	Comment
Tuberculosis incidence rate	9	Critical

2. Literature search strategy and information retrieval

Studies were identified using PubMed and the Cochrane Library databases. No systematic reviews were identified using the Cochrane database.



Selection criteria

Studies were selected if:

- *randomized and quasi-randomized controlled studies, including historically controlled trials or observational and cohort studies;*
- *participants were people living with HIV;*
- *incidence rates for both exposure groups of PICO question were given.*

*Excluded observational studies:

- *Tuberculosis incidence rate was not an outcome: Ai Lian (2007), Detels (2001), Eng (2009), Girardi (2000), Losina (2007) and Santaro-Lopes (2002);*
- *Person-years for study arms not included: Lannoy (2008) and Miranda (2007);*
- *Intervention was not ART: Brodt (1997), Dore (2002), Elzi (2007), Gillini (2002), Ives (2001), Kirk (2000) and Muga (2007).*

Investigators in the field were contacted by email. The NA-ACCORD and HIV-CASUAL collaborations shared abstracts which were included. ART-CC updated the data from their study which were included (Girardi et al., 2005). Three relevant studies which were not captured by the MEDLINE search were also included (Golub et al., 2007, Severe et al., 2010, Cohen et al., 2011). Therefore, five additional studies were added to the six studies identified by the literature search.

Table 1 summarizes the findings from the 11 studies meeting eligible criteria for the review. ART causes immune reconstitution, prevents the development of opportunistic infections and prevents other HIV-related conditions. Data from observational cohorts have demonstrated the benefits of ART in reducing rates of TB (*1–3*). Data from South Africa show that TB rates decrease in a stepwise fashion as a result of ART-induced immune reconstitution, with high rates persisting until CD4 counts recover to more than 500 cells/mm^3 (*4*). The rates of TB for South Africans with CD4 counts less than 100 cells/mm^3 were approximately 10 times the rate of South Africans with CD4 counts exceeding 500 cells/mm^3. HIV-infected South Africans with CD4 counts more than 500 cells/mm^3 had about a two-fold increased rate of TB compared with HIV-negative persons. Many people living with HIV in Africa start ART with CD4 counts less than 100 cells/mm^3 (*5*). WHO treatment guidelines published in 2010 recommend initiating ART at CD4 counts ≤350 cells/mm^3 regardless of the presence of signs and symptoms (*6*). Data from observational studies assessed in this review and that did not specify CD4 counts showed that ART halves TB incidence rates. When ART is used in CD4 count stratum 200–350 cells/mm^3, TB incidence is reduced up to 88% in observational studies (*7, 8*) and by half in randomized controlled trials (*9*). In CD4 stratum >350 cells/mm^3, ART use reduces TB incidence rates by up to 75% in observational studies (*7, 8*) and by half in randomized controlled trials (*10*). TB case ascertainment was either definite (culture-confirmed TB) or probable (AFB smear-positive or signs, symptoms and chest radiography consistent with TB or histological finding of caseating/necrotizing granulomas or clinical response to antituberculosis treatment). Observational studies also showed a greater reduction in TB risk (up to 90%) among patients receiving both ART and IPT (*11, 12*).

Table 1: Summary of studies on antiretroviral therapy (ART) for prevention of tuberculosis (TB)

Author (Year)	Methods/ design	Population	Participants	Intervention	Follow-up	TB episodes and case ascertainment
Badri (7) (2002)	Observational cohort	HIV patients attending New Somerset Hospital adult HIV clinic, University of Cape Town, between 1992 and 2001. This is a major public health-care facility.	Inclusion: aged >15 years. Exclusion: acute opportunistic infection, significant laboratory abnormalities, current evidence of active substance abuse, pregnancy or lactation, TB at baseline visit, use of IPT in the 6 months prior to baseline, and treatment with immune-modulating or systemic chemotherapeutic agents	HAART (defined as 2 NRTIs plus one of the following: (i) an NNRTI, (ii) a PI, or (iii) a third NRTI)	For patients on ART, every 2–3 months, clinical, immunological and virological information was taken, or more frequently if clinically indicated. For patients not on ART, follow-up was every 3–6 months. Mean follow-up in those exposed to ART was significantly greater than in the controls (16.8 (SD 8.3) vs 13.2 (SD 15.5) months).	2 cases during 100.1 person-years on ART with baseline CD4 counts >350 cells/mm^3; 14 cases during 388.3 person-years off ART with baseline CD4 counts >350. Adjusted RR was 0.36 (95% CI 0.10 to 1.74) for this CD4 stratum. 2 cases during 121.2 person-years on ART with baseline CD4 counts 200–350; 27 cases during 225 person-years off ART with baseline CD4 counts 200–350. Adjusted RR was 0.12 (95% 0.03 to 0.53) for this CD4 stratum. Across all CD4 strata, of the 9 TB cases on ART, 5 were definite (culture/autopsy confirmed) and 4 were probable (presence of AFB or histological finding of caseating granulomata). Of the 82 TB cases off ART, 48 were probable and 34 were definite.
del Amo (8) (2011)	Observational cohort	This analysis from the HIV-CAUSAL Collaboration includes 11 observational cohorts from 1996 to 2007. The cohorts are in the UK, the Netherlands, France, Spain and the USA.	HIV-infected individuals who were aged ≥18 years, antiretroviral naive, without AIDS, not pregnant, and in whom CD4 counts and viral load were measured within 6 months of each other at baseline. Individuals with TB during the first month of follow up were excluded (prevalent TB case).	Combined ART (defined as a regimen including >3 ARTs, 2 ritonavir-boosted PIs, or 1 NNRTI and 1 boosted PI)	For each patient, follow-up ended at the earliest of: TB diagnosis, death, 12 months after the most recent laboratory measurement, pregnancy (if known), or the cohort-specific administrative end of follow-up.	The overall hazard ratio of TB for combined ART was 0.56 (95% CI 0.44–0. 72). The hazard ratios were similar for individuals with baseline CD4 counts >350 (0.50, 95% CI 0.36–0.69) and 200–350 (0.45, 95% CI 0.27, 0.74). TB cases were diagnosed according to standard clinical practice in Europe and the USA.
Girardi (13) (2005)	Observational cohort	The ART Cohort Collaboration (ART-CC) is an international collaboration of cohort studies from Europe and North America. This study included 12 cohorts.	Antiretroviral-naive subjects had to be aged ≥16 years. Data were from subjects who started ART between 1996 and 2008 (ART-CC updated the data presented in the 2005 article). Follow-up was censored at 3 years from start of ART	HAART (defined as at least 3 drugs, including PIs, NNRTIs and NRTIs)	Data on HAART regimen (PI/NNRTI/NRTI-based), CD4 count, viral load, gender, age, year of HAART initiation and risk group (MSM, injection drug user, heterosexual, blood-product recipient, other/not known) were collected	676 cases during 124 669 person-years on HAART with baseline CD4 counts ≤350; 58 cases during 23 420 person-years on HAART with baseline CD4 counts 351–500. The IRR was 0.46 (95% CI 0.35, 0.60) for higher vs lower baseline CD4 counts at HAART initiation. All TB cases underwent antituberculosis treatment. Since the standard of medical care is to confirm TB prior to starting antituberculosis treatment, investigators indicate that all the TB cases were culture-confirmed.

Table 1: Summary of studies on antiretroviral therapy (ART) for prevention of tuberculosis (TB)

Author (Year)	Methods/ design	Population	Participants	Intervention	Follow-up	TB episodes and case ascertainment
Golub (*12*) (2009)	Observational cohort	HIV patients receiving primary HIV care at two clinics affiliated with the University of the Witwatersrand: the Perinatal HIV Research Unit (PHRU) in Soweto, a large, urban setting, and the Tintswalo Hospital, a remote, rural clinic in Mpumalanga Province.	HIV-infected adults aged >18 years. No exclusion criteria listed	HAART (not defined) and/or IPT	Time between visits is scheduled to be 4–7 months, but patients may visit the clinic at any time. Follow-up data collection focuses on clinical diagnoses, symptoms and longitudinal data including height and weight, smoking status, alcohol consumption and measures of socioeconomic status. Laboratory tests include CD4 and full blood counts at recruitment and every 6 months.	200 cases of TB during 2815 unexposed person-years; 44 cases during 952 person-years on HAART; 1 case during 93 person-years on IPT and ART. The IRR for HAART was 0.65 (0.46–0.91). The IRR for IPT and HAART was 0.15 (0.00–0.85). The adjusted HR for HAART was 0.36 (0.25, 0.51). The adjusted HR for IPT and HAART was 0.11 (0.02, 0.78).
Golub (*11*) (2007)	Observational cohort	Baseline medical records were analysed for a 2-year period (from 1 September 2003 to 1 September 2005) in 29 public clinics in Rio de Janeiro, Brazil.	Patients who had made at least one visit to one of the clinics (from 1 September 2003 to 1 September 2005) and who received their primary care from the clinics were included. Patients who attended the clinic to collect antiretroviral medications prescribed by a private physician were excluded, as were patients who died before 1 September 2003.	ART (not defined) and/or IPT	Follow-up ended at TB diagnosis or the earlier of their last visit to an HIV clinic, the date of administrative censoring or death. Information collected included age, sex, date of HIV diagnosis, treatment history (antiretroviral drugs, IPT), dates of opportunistic diseases including TB, and results of diagnostic tests including CD4 counts, HIV viral loads and TST.	155 cases during 3865 unexposed person-years; 221 cases during 11627 person-years on ART; 10 cases during 1253 person-years on ART and IPT. IRR for ART was 0.48 (0.39, 0.59). IRR for ART and IPT was 0.20 (0.09, 0.91). Adjusted HR was 0.41 (0.31, 0.54) for ART. Adjusted HR was 0.24 (0.11, 0.53) for ART and IPT.
Jones (*14*) (2000)	Observational cohort	The Adult/Adolescent Spectrum of HIV Disease project is a multicentre observational cohort study including sites in Atlanta, GA; Dallas, Houston, and San Antonio, TX; Denver, CO; Detroit, MI; Los Angeles, CA; Seattle, WA; New Orleans, LA; New York, NY; and Bayamon, Puerto Rico.	HIV-infected persons are identified at their first health-care encounter regardless of the stage of their HIV infection. All patients aged >13 years who were infected with HIV and who attended participating clinics during the study period were eligible for enrolment.	HAART (defined as triple therapy with 2 NRTIs and an NNRTI or PI, or any combination including a PI)	On successive 6-month follow-up intervals, medical records are reviewed for illnesses, AIDS-defining conditions, prescriptions, laboratory tests and medical care utilization. TB incidence was assessed by examining the first prospective occurrence of TB from January 1996 to June 1998.	45 cases during 6250 unexposed person-years; 7 cases during 3684 person-years on HAART. The IRR was 0.2 (0.1, 0.5).

Table 1: Summary of studies on antiretroviral therapy (ART) for prevention of tuberculosis (TB)

Author (Year)	Methods/ design	Population	Participants	Intervention	Follow-up	TB episodes and case ascertainment
Lau (*15*) (2010)	Observational cohort	The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) includes 22 research groups, representing more than 60 study sites.	HIV-infected patients who received medical care between January 1996 and December 2005 and had no history of an AIDS-defining illness and were ART-naive.	HAART (defined as a regimen containing at least 3 ART drugs, one of which had to be a PI, an NNRTI, abacavir/ tenofovir, an integrase inhibitor , or maraviroc/ enfuvirtide)	Individuals contributed person-time starting from the month of initiation of HAART up until TB diagnosis, loss to follow-up (last contributed CD4 count), or administrative censoring.	124 cases during 149 011 person-years on HAART with baseline CD4 counts ≤350; 13 cases during 27 601 person-years on HAART with baseline CD4 counts 351–500. The IRR was 0.57 (95% CI 0.32, 1.00) for earlier HAART; 8 cases during follow-up for persons on HAART with baseline CD4 counts >500. Of the 145 TB cases, 98 were culture-positive, 39 were culture-negative and 8 were of unknown culture status. For the TB cases that were not positive, TB diagnosis was established by signs, symptoms and chest radiography consistent with TB, pathology with necrotizing granulomas and AFB, positive NAAT and/or clinical response to antituberculosis therapy.
Ledergerber (*16*) (2000)	Observational cohort	The Swiss HIV Cohort Study enrols HIV-infected persons aged >16 years in Basel, Bern, Geneva, Lausanne, Lugano, St Gall and Zurich.	All participants who started potent ART between September 1995 and December 1997; had a CD4 count and a viral load during the 3 months before starting; and made ≥1 follow- up visit >1 month after starting ART.	Potent ART (defined as combination treatment with at least 3 drugs, including at least 1 PI)	Data are collected at 6-month intervals. Medications are registered by month of initiation and discontinuation.	7 cases during 897 unexposed person-years; 6 cases during 2727 person-years on ART. The IRR was 0.28 (95% CI 0.09, 0.84).
Moreno (*17*) (2008)	Observational cohort	CoRIS-MD is an open multicentre hospital-based cohort study within Spain's HIV Research Network of Excellence.	All HIV-infected subjects aged >18 years, with at least 6 months of follow-up, seen at any time between 1 January 1997 and 30 June 2003 in any of the participating centres.	HAART (defined as ART regimens including 2 NRTIs plus either an NNRTI or a PI, or 3 NRTIs)	Data were collected for: sex, age, transmission category, period of observation, CD4 count, viral load, AIDS diagnosis, treatment status at entry and over time, and vital status. Median follow-up was 4.1 years (IQR, 2.0–6.4) in HAART-naive and 2.9 years (1.5–4.6) in HAART.	129 cases during 5215 unexposed person-years; 75 cases during 7825 person-years on HAART. The IRR was 0.26 (95% CI 0.16, 0.40).

Table 1: Summary of studies on antiretroviral therapy (ART) for prevention of tuberculosis (TB)

Author (Year)	Methods/ design	Population	Participants	Intervention	Follow-up	TB episodes and case ascertainment
Cohen (*10*) (2011)	Randomized controlled trial	The trial had global representation with 13 sites in Botswana, Brasil, India, Kenya, Malawi, South Africa, Thailand, the United States and Zimbabwe.	HIV-serodiscordant couples in which the HIV-infected partner is ART-naive and has a CD4 count between 350 and 550 cells/mm^3	The ART regimens in this study were consistent with WHO guidelines	All participants completed monthly follow-up visits throughout the study. For those on ART, laboratory and adherence measurements took place. For those not on ART laboratory and counselling took place.	33 cases among the 877 adults initiating ART with CD4 counts <350 cells/μL; 17 cases among the 886 people initiating ART with CD4 counts >350 cells/μL. This translated into an RR 0.51 (0.28–0.91).[a]
Severe (*9*) (2010)	Randomized controlled trial	The study was conducted at the centre of the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections in Port-au-Prince, Haiti	HIV-infected participants aged ≥18 years with CD4 counts from 200 and 350 cells/mm^3 within 45 days before enrolment were included. Participants with a history of an AIDS-defining illness or who had received ART previously were excluded	Treatment included lamivudine, zidovudine, and efavirenz	Adherence was measured every 6 months using a questionnaire. Adverse events were monitoring using DAIDS criteria. Complete blood count, liver enzyme tests and serum chemical tests were repeated every 3 months for participants on ART. CD4 results were collected 6-monthly.	36 cases of TB among the 393 people who were randomized to defer ART until their CD4 counts were <200; 18 cases of TB among the 380 people who were randomized to initiate ART immediately (i.e. between 200 and 350). This translated into an RR of 0.52 (0.30–0.89).[b]

AFB, acid-fast bacilli; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IPT, isoniazid preventive therapy; IQR, interquartile range; IRR, incidence rate ratio; NAAT, nucleic acid amplification test; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RR, risk ratio; SD, standard deviation; TB, tuberculosis; TST, tuberculin skin test

a The AIDS Clinical Trials Group definition for confirmed or probable TB was used:

- Confirmed pulmonary TB: *Mycobacterium tuberculosis* cultured from sputum, broncho-alveolar lavage fluid or lung tissue.
- Probable pulmonary TB: (i) clinical syndrome consistent with pulmonary TB, including >1 of the following: fever >38 °C, night sweats, productive cough, haemoptysis, weight loss; *and* (ii) AFB smear from sputum, gastric aspirate, broncho-alveolar lavage fluid or lung tissue; or AFB identified on histopathology of lung tissue and *M. avium* complex and other atypical mycobacteria excluded; *and* (iii) abnormal chest X-ray consistent with pulmonary TB; *and* (iv) specific multi-drug antituberculous therapy initiated.
- Confirmed extrapulmonary TB: positive culture for *M. tuberculosis* from extrapulmonary site.
- Probable extrapulmonary TB: (i) positive AFB smear or a positive histopathology from an extrapulmonary site; *and* (ii) >1 of the following signs or symptoms consistent with a clinical syndrome for extrapulmonary TB: fever >38 °C, night sweats, malaise, weight loss and/or adenopathy; *and* (iii) specific multi-drug antituberculous therapy initiated.

b The American Thoracic Society's case definition was used: two of the following three criteria were met: (i) >1 of fever (temperature >38 °C) for at least 1 week, night sweats for at least 1 week, weight loss (>10% bodyweight), cough, dyspnoea, haemoptysis or lymphadenopathy for at least 4 weeks; (ii) AFB visible in sputum, *M. tuberculosis* cultured from sputum, or histopathological findings in biopsy samples consistent with mycobacterial disease; *and* (iii) a chest radiograph interpreted as highly suggestive of TB by two independent radiologists. Clinical response to antituberculosis medications was defined as resolution of clinical symptoms and signs, and a 50% decrease in the size of the effusion, infiltrate or hilar adenopathy at 8 weeks, as judged by an independent radiologist.

3. GRADE profile

The quality of evidence across a body of evidence was assessed using the GRADE approach. For systematic reviews, the GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest.

The quality rating across studies has four levels: high, moderate, low, or very low. Randomized trials are categorized as high quality but can be downgraded. Observational studies are categorized as low but can be upgraded. Factors that decrease the quality of evidence include design limitations, inconsistency among studies, indirectness of evidence and imprecision of effect measures, among other biases. Factors that can increase the quality level of a body of evidence include a large magnitude of effect, plausible confounding reducing a demonstrated effect and a dose-response gradient.

The GRADE Profiler software was used to perform the GRADE analyses (GRADE profiler version 3.2.2).

Table 2: Should antiretroviral therapy (ART) be used to prevent active tuberculosis (TB)?

Settings: All

Bibliography: Badri et al. (2002), Cohen et al. (2011), del Amo et al. (2011), Golub et al. (2007), Golub et al. (2009), Jones et al. (2000), Ledergerber et al. (1999), Moreno et al. (2008), Severe et al. (2010)

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ART	Control	Relative (95% CI)	Absolute	Quality	Importance
TB incidence, baseline CD4 counts 200–350 (observational)												
2	Observational studies[1]	No serious limitations	No serious inconsistency	Serious indirectness[2]	No serious imprecision	Strong association[3]	Not reported	Not reported	RR 0.39 (0.24–0.63)[4]	Not estimated since rate data used	LOW	CRITICAL
TB incidence, baseline CD4 counts 200–350 (randomized controlled trials)												
1	Randomized controlled trial[5]	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	18/380	36/393	RR 0.52 (0.30–0.89)[6]	44 fewer per 1000 (from 10 fewer to 64 fewer)	HIGH	CRITICAL
TB incidence, baseline CD4 counts >350 (observational)												
2	Observational studies[1]	No serious limitations	No serious inconsistency	Serious indirectness[2]	No serious imprecision	Strong association[3]	Not reported	Not reported	RR 0.49 (0.36–0.68)[4]	Not estimated since rate data used	LOW	CRITICAL
TB incidence, baseline CD4 counts >350 (randomized controlled trials)												
1	Randomized controlled trial[7]	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	17/886	33/877	RR 0.51 (0.29–0.91)[6]	18 fewer per 1000 (from 3 fewer to 27 fewer)	HIGH	CRITICAL
TB incidence, baseline CD4 counts not provided												
5	Observational studies[8]	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association[2]	132/15188 (0.9%)[9]	381/15177 (2.5%)[9]	RR 0.47 (0.41–0.53)[4]	Not estimated since rate data used	MODERATE	CRITICAL
TB incidence, ART and IPT (baseline CD4 counts not provided)												
2	Observational studies[10]	serious[11]	No serious inconsistency	No serious indirectness	No serious imprecision	Very strong association[12]	11/1346 (0.8%)[9]	355/6680 (5.3%)[9]	RR 0.15 (0.08–0.28)[4]	Not estimated since rate data used	MODERATE	CRITICAL

1 del Amo et al. (2011) and Badri et al. (2002).
2 del Amo et al (2011) study conducted in Europe and North America, settings with low TB transmission.
3 Large magnitude of effect as defined by GRADE (RR estimate <0.5).
4 The measure of effect is an incidence rate ratio.
5 Severe et al. (2010).
6 The measure of effect is a risk ratio.
7 Cohen et al. (2011).
8 Golub et al. (2007), Golub et al. (2009), Moreno et al. (2008), Ledergerber et al. (2000), and Jones et al. (2000).
9 Numerator is TB cases, denominator is person-years at risk.
10 Golub et al. (2007) and Golub et al. (2009).
11 Antiretroviral therapy not defined in either study (Golub et al. 2007 and Golub et al. 2009).
12 Very large magnitude of effect as defined by GRADE (RR estimate <0.2).

4. Risk and benefits assessment

Recommendation: People living with HIV with CD4 counts >350 cells/mm^3 should receive ART to prevent active TB

Population: People living with HIV with CD4 counts >350 cells/mm^3

Intervention: Antiretroviral therapy

Factor	Decision	Explanation
Quality of evidence	High	The reduction in tuberculosis incidence is supported by HIGH quality randomized trial evidence
Benefits or desired effects	Strong (benefits outweigh risks)	Reduction in tuberculosis incidence. Additional benefits of ART in reducing mortality, other HIV related morbidity, and HIV transmission
Risks or undesired effects		Reduction in tuberculosis incidence. Additional benefits of ART in reducing mortality, other HIV related morbidity, and HIV transmission
Values and preferences	Variable	Improved quality of HIV treatment and care. Also prevents life-threatening opportunistic infections, increases survival, and prevents HIV transmission to others Life-long therapy with issues of adherence and side effects in the long term. High pill burden when ART taken with other preventive or curative treatment.
Costs	Weak	Costs will increase as the volume of patients will at least double, with impact on drug and non-drug costs. Evidence on long run cost savings only demonstrated by mathematical modelling. Cheaper interventions exist such as isoniazid preventive therapy which is yet to be scaled-up
Feasibility	Weak	A move to CD4 threshold >350 for ART initiation will at least double the number of eligible patients to start ART. In a context of low uptake, late presentation for treatment and limited resources in majority of high HIV prevalence settings, it can generate confusing messaging, competing forces in terms of infrastructure demand and very serious issues of equity towards patients with lower CD4 counts and who have not accessed yet ART
Not recommended		

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Annex 2

Voluntary counselling and testing for HIV benefits patients with diagnosed and presumptive tuberculosis – summary of findings and evaluation of the quality of the evidence

PICO question: What are the benefits of HIV testing and counselling in patients with presumptive and diagnosed tuberculosis and among the partners and family members of patients who are found to be HIV-positive?

Population: people with presumptive and diagnosed TB, and the partners and family members of patients who are found to be HIV positive

Intervention: HIV testing and counselling

Comparison: no HIV testing and counselling

Outcomes: yield of positive HIV cases

1. Outcomes of interest

Outcomes	Relative importance (rank 1 → 9 most critical)	Comment
Among presumptive and confirmed TB patients		
HIV cases (yield of positive HIV and TB cases by clinical settings and by epidemiological settings)	9	critical
Improved access to prevention, care and treatment (reduced morbidity and mortality events due to TB and HIV diseases)	9	critical
Among partners and family members		
HIV cases	9	critical
Improved access to prevention, care and treatment	8	critical

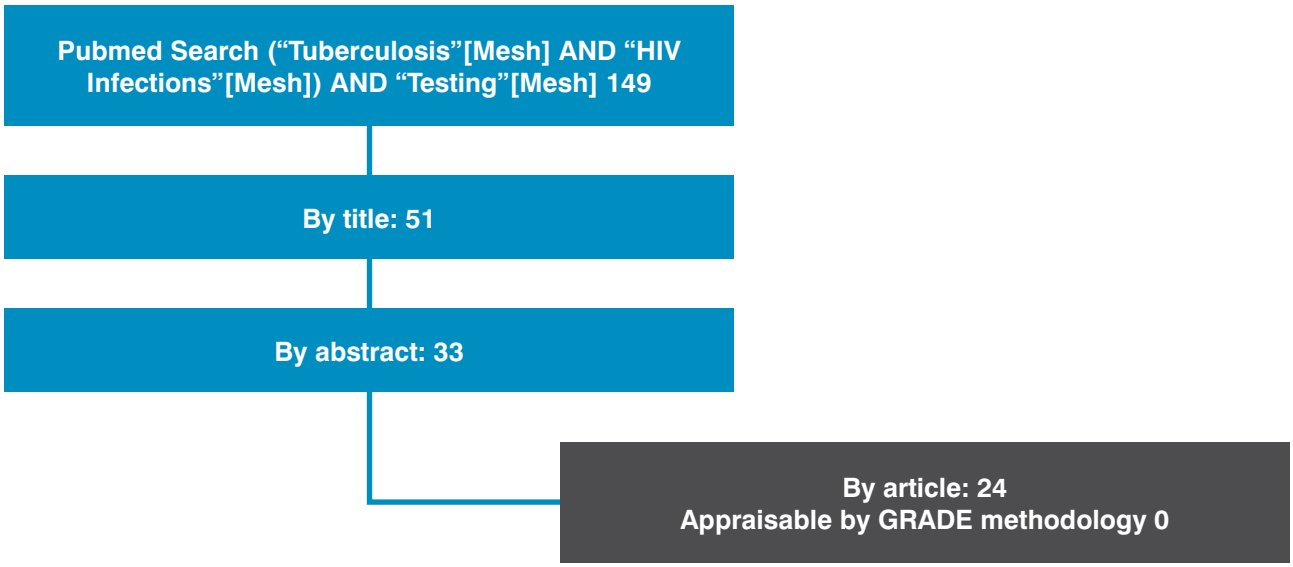
2. Literature search strategy and information retrieval

Studies were identified using PubMed, EMBASE, Web of Science, Google Scholar and the Cochrane Library databases. Proceedings and abstracts from international conferences (CROI, IAS, ICAAC, World AIDS Conference) were searched.

Selection criteria

Studies were included if:

- *randomized and quasi-randomized controlled trials, including historically controlled trials or observational and cohort studies;*
- *participants being presumed or confirmed TB cases or/and partners and family members of those who turn to be HIV positive;*
- *comparison being addressed was: routine HIV testing vs. no HIV testing.*



Most data that can be found on this topic is circumstantial evidence, most likely because it is deemed unethical to compare groups in which HIV testing is offered against one in which it is not. This would deprive people of the right to then make choices about treatment.

The only study which has a comparison group was carried out in Malawi and compared patients after the introduction of voluntary counselling and testing (VCT) and co-trimoxazole prophylaxis therapy (CPT) to patients before (*1*); unfortunately, there was no stratification and therefore it is not amenable to GRADE appraisal.

It is now clear that people with HIV-associated TB fare a lot worse than those with HIV or TB separately. Treatment for HIV is becoming increasingly available, and evidence shows that even just CPT is beneficial in decreasing morbidity and mortality. Knowledge of HIV status is also beneficial for sexual partners and unborn children. Thus it is hard to imagine the need for evidence to be collected to prove that testing patients with TB for HIV is beneficial.

A large number of studies show that testing for HIV in confirmed TB patients (mostly) and in presumptive TB patients and their contacts (occasionally) yields a high number of new diagnoses of HIV. The assumption is that this allows newly diagnosed HIV-positive people to receive CPT and ART, thus hypothetically decreasing their morbidity and mortality and preventing HIV transmission. These same descriptive studies also show that often after diagnosis, either the HIV treatment is not offered or available, or it is not taken up. According to the HIV/AIDS universal access report, only 17% of the estimated number of TB patients living with HIV were receiving ART, a figure considerably lower than the estimated coverage rate of antiretroviral therapy for all HIV patients in low- and middle-income countries (*2*).

Table 1 summarizes the 24 studies retrieved from the systematic literature search. It shows that in these studies HIV testing in TB patients can yield positive results anywhere between 6.3% and 77% depending on the epidemiologic setting. Although 6.3% appears low, consideration should be given to the fact that HIV is a transmissible, 100% fatal disease without available treatment and prevention measures. A few of the studies addressed the issue of contacts or cases with presumptive TB, although they yield very little data. In one study carried out in Kenya on presumptive TB patients, 61% diagnosed with TB were also HIV-positive, whereas 63% without TB were positive (*3*). Another study in Uganda (*4*) found that 39% patients diagnosed with TB were also HIV-positive, whereas 49% of those who had no active TB were HIV-positive. The yield of HIV-positive results among those with presumptive TB was 39% in Guinea-Bissau and 61% in Zimbabwe (*5, 6*).

Only one study addressed the issue of testing close contacts of TB patients and on doing so found that 13.8% of contacts of TB patients living with HIV were HIV-infected, whereas 2.5% of contacts of HIV-negative TB patients were HIV-infected (*7*). One study attempted to quantify the benefit of testing by looking at relative risk of death of a cohort of patients in one programme before and after the introduction of VCT (*1*). It found the adjusted relative risk of death to be 0.81 ($p<0.001$).

Table 1: Summary of studies on testing for HIV infection in TB patients, people with suspected TB and contacts of TB patients

Author and year (reference)	Country	Background HIV prevalence (14–59years)	Type of study	Sample size	Testing site and personnel	HIV testing uptake	% tested HIV-positive	CPT uptake	ART uptake
Ayenew A, 2010 (*8*)	Ethiopia	2%	Case-control	282 TB patients	–	70.6%	36.2%	–	–
Njozing NB, 2010 (*9*)	Cameroon	5.1%	Retrospective cohort	2270 TB patients	Counsellors within TB units	94.7%	68.5%	47%	50.3%
Vijay S, 2009 (*10*)	India	0.3%	Prospective cohort	5299 TB patients (4701 unknown HIV status)	Physician referral to integrated counselling and testing centres	66%	6.4% (of previously undiagnosed)	–	37%
Low SY, 2009 (*11*)	Singapore	0.2%	Retrospective	493 TB patients	–	37.3%	8.2%	–	–
Nateniyom S, 2008 (*12*)	Thailand	1.4%	Prospective cohort	1086 TB patients (1000 unknown HIV status)	Trained nurses and social workers in TB clinics	93%	11%	36%	42%
Pope DS, 2008 (*13*)	South Africa	18.1%	Cluster-randomized	754 TB patients	TB nurse in TB clinic	13.8%	36–42%	19%	21%
Van Rie A, 2008 (*14*)	Democratic Republic of the Congo		(opt-in vs opt-out)	1246 TB patients	VCT clinic vs primary care centre vs TB nurse	95–98%	18.8%	89.8%	–
Chakaya JM, 2008 (*15*)	Kenya	7.1-8.3%	Retrospective cohort	46428 TB patients	Health-care workers in TB care services	31.5–59%	55%	85%	28%
Morbidity and Mortality Weekly Report, 2008 (*16*)	Zambia	13.1%	Descriptive	4148 TB patients	VCT offsite, VCT onsite, PITC by TB staff	50%	72%	–	–

Table 1: Summary of studies on testing for HIV infection in TB patients, people with suspected TB and contacts of TB patients

Author and year (reference)	Country	Background HIV prevalence (14–59years)	Type of study	Sample size	Testing site and personnel	HIV testing uptake	% tested HIV-positive	CPT uptake	ART uptake
Jerene D, 2007(*17*)	Ethiopia	2%	–	190 TB patients	Trained counsellor at TB clinic in hospital	58%	20.6%	–	–
Morbidity and Mortality Weekly Report, 2006 (*18*)	Guyana	–	Descriptive	174 TB patients of unknown status	–	91%	10%	–	–
van der Werf MJ, 2005 (*19*)	Ukraine	–	Prospective	914 TB patients	TB physicians	84%	6.3%	–	–
Chimzizi RB, 2004 (*20*)	Malawi	12%	Evaluation of project	2397 TB patients	Counsellors in laboratory, ward or VCT unit	59%	68%	97%	–
Chimzizi RB, 2004 (*21*)	Malawi	12%	Descriptive	1103 TB patients	Counsellors in laboratory, ward or VCT unit	91%	77%	69%	
Zachariah R, Jan 2003 (*22*)	Malawi	12%	Cohort study	1049 TB patients	Hospital HIV VCT unit	91%	77%	94%	
Zachariah R, May 2003 (*1*)	Malawi	12%	Cohort study	1986 TB patients	Hospital HIV VCT unit	91%	77%	93%	
Abouya L, 1998 (*23*)	Côte d'Ivoire	–	Cohort study with historical controls	19594 TB patients	Physicians, nurses and social workers	91.8%	43.2%	–	–
Banerjee A, 1997 (*24*)	Malawi	12%	Retrospective	205 TB patients	–	54%	66%	–	–

Table 1: Summary of studies on testing for HIV infection in TB patients, people with suspected TB and contacts of TB patients

Author and year (reference)	Country	Background HIV prevalence (14–59years)	Type of study	Sample size	Testing site and personnel	HIV testing uptake	% tested HIV-positive	CPT uptake	ART uptake
Studies including presumptive TB patients									
Porskrog A, 2011 (*6*)	Guinea-Bissau	9%	Prospective cohort	86 with presumptive TB	VCT unit	51%	39%	–	–
Dimairo M, 2010 (*5*)	Zimbabwe	–	Prospective cohort nested within cluster randomized trial	1195 with presumptive TB	VCT unit and study clinic	95%	61%	–	15%
Odhiambo J, 2008 (*3*)	Kenya	7.1–8.3%	Pilot study-descriptive	5457 with presumptive TB	Clinical officers and TB nurses in TB clinics	89%	61–63%	–	83%
Srikantiah P, 2007 (*4*)	Uganda	5.4%	Prospective cohort	665 with presumptive TB	Trained counsellors at TB clinic	85%	42%	–	–
Munthali L, 2006 (*25*)	Malawi	12%	Cross-sectional survey	565 with presumptive TB	–	95%	56%	–	–
Studies including contacts									
Suggaravetsiri P, 2003(*7*)	Thailand	1.4%	Descriptive	499 TB patients 1200 TB contacts	–	74.2%	39.5% 13.8% (if contact case HIV-positive) 2.5% (if case HIV-negative)	–	–
Ranges						13.8–98%	6.3–77%		21–83%

ART, antiretroviral therapy; CPT, co-trimoxazole preventive therapy; PICT, provider initiated counselling and testing; VCT, voluntary counselling and testing; %, percentage

In all studies, the prevalence of HIV was found to be higher in TB patients, those with presumptive TB and possibly even among TB contacts than the expected national adult HIV prevalence. One study highlighted higher rates of mortality among HIV-positive TB patients (29%) compared to those with TB only (8%) (*24*). Interestingly, 34% of those who refused testing died, but a possible bias is that anybody very unwell and suspicious of having HIV is possibly more likely not to test.

3. GRADE profile

The quality of evidence across a body of evidence was assessed using the GRADE approach but risk ratios could not be calculated as none of the studies available assessed the question of interest. GRADE profiles were therefore not produced.

4. Risk and benefits assessment

Recommendation: Routine HIV testing should be offered to all patients with presumptive and confirmed TB, their partners and family members		
Population: TB patients, patients with presumptive TB, and their partners and family members		
Intervention: Routine HIV testing		
Factor	**Decision**	**Explanation**
Quality of evidence	Low	There is a wealth of evidence documenting that TB and HIV coinfection has a worse outcome than TB alone. There is plenty of evidence that the population in question (patients with presumptive and confirmed TB) has a high prevalence of HIV and that those with HIV have high prevalence of TB. There is little evidence that contacts of HIV-positive TB patients have high prevalence of HIV. Unfortunately, there are no randomized controlled trials or high-quality studies for GRADE appraisal.
Benefits or desired effects	Strong	Knowledge about status is a prerequisite for HIV prevention, treatment, care and support, including CPT and ART, which reduce morbidity and mortality. Even those who test negative have increased awareness, allowing them to avoid risk-taking behaviour, promote safer sexual behaviour and practices, and encourage their partners to do the same and/or be on ART and anti-TB treatment if indicated.
Risks or undesired effects		False-positive results; false negative results. Stigma of HIV diagnosis once known.
Values and preferences	Strong	Improved individual and family care Better health for individual, partners, family and community Prevent HIV transmission to loved ones Stigma and problem of disclosure might lead to low uptake
Costs	Strong	Testing using rapid tests is inexpensive and incorporated in health package. Savings by decreasing HIV and TB transmission and resulting morbidity and mortality.
Feasibility	Strong	Structure for testing already in place and working. Increased workload on health workers – actually less in the long term if fewer people have TB and HIV Feasibility studies from India and Rwanda showed that it is feasible to routinely test TB patients for HIV (*26, 27*)
Strength of recommendation **Strong**		

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Annex 3

Co-trimoxazole preventive therapy (CPT) reduces morbidity and mortality in tuberculosis patients living with HIV – summary of findings and evaluation of the quality of the evidence

PICO question: Does the administration of routine CPT compared with no CPT reduce the number of illness episodes and deaths in TB patients living with HIV?

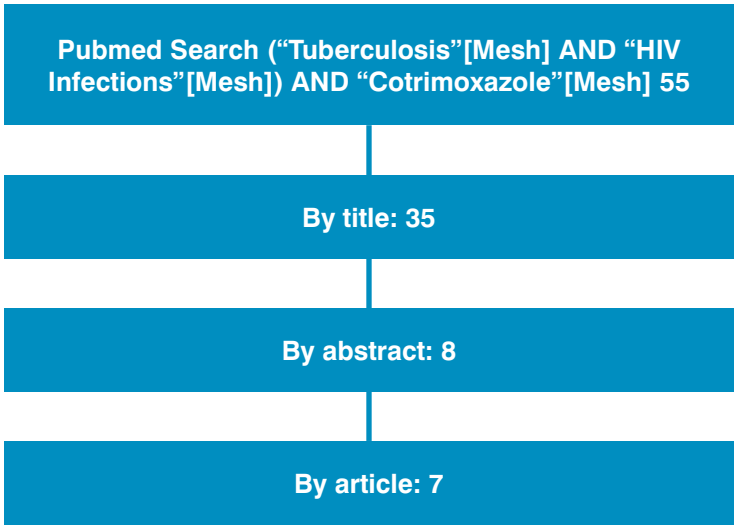
Population: TB patients living with HIV
Intervention: CPT
Comparison: no CPT or placebo
Outcomes: mortality, morbidity/hospital admissions/adverse events

1. Outcomes of interest

Outcomes	Relative importance (rank 1 → 9 most critical)	Comment
Mortality (deaths occurring during the follow up period)	9	Critical
Morbidity/hospital admissions (as defined by the trial researchers)	9	Critical
Adverse events (leading to hospitalization or treatment cessation)	9	Critical

2. Literature search strategy and information retrieval

Studies were identified using PubMed, EMBASE, Web of Science, Google Scholar and the Cochrane Library databases. Proceedings and abstracts from international conferences (CROI, IAS, ICAAC, World AIDS Conference) were searched.



Selection criteria

Studies were selected if:

- *randomized and quasi-randomized controlled trials, including historically controlled trials or observational and cohort studies;*
- *participants being people living with HIV with active TB (studies that include participants both with and without active TB disease were considered where the data for those with TB disease could be extracted);*
- *comparison being addressed was: routine CPT vs. placebo or no CPT.*

Table 1 summarizes the findings from the two randomized controlled trials (RCTs) and the six observational studies, using historical controls or observational cohorts, identified by the systematic literature search. All studies were conducted in Africa.

Co-trimoxazole, a fixed-dose combination of sulfamethoxazole and trimethoprim, is a broad-spectrum antimicrobial agent that has been used since the mid-1980s to prevent *Pneumocystis jirovecci* pneumonia and toxoplasmosis in people living with HIV. It is also effective against other bacterial and parasitic diseases and it reduces the incidence of malaria in people living with HIV.

Data on CPT among TB patients living with HIV showed that survival of those receiving CPT is improved up to 18 months after diagnosis of TB disease in observational studies and up to 24 months of follow-up in one of the two RCTs (*1*). The number needed to treat to prevent one death during TB treatment was 24 in one observational study using historical controls conducted in South Africa (*2*) and 12.5 in another cohort study evaluating the benefit of a combination of HIV testing and provision of CPT in Malawi (*3*). All studies showed that adverse reactions, defined as those causing cessation of CPT or hospitalization, were infrequent with few patients having to definitely stop prophylaxis. Only one RCT studied the effect of CPT on morbidity through hospital admission for all diseases that could potentially have been prevented by CPT (septicaemia, enteritis, chest infection, urinary tract infection and toxoplasmosis) (*4*). The rate of admissions was significantly lower in the co-trimoxazole group (2.7/100 person-years) than in the placebo group (8.7/100 person-years; P=0.001). This trial also showed that the mortality rate was significantly lower in patients with CD4 counts ≤350 cells/mm^3 receiving CPT than those receiving a placebo (hazard ratio: 0.44, 95% CI: 0.29–0.66). There is also a wealth of evidence on the benefits of CPT in reducing mortality and morbidity among people living with HIV without TB and their household members.

Table 1: Summary of studies on co-trimoxazole preventive therapy (CPT) in HIV-infected TB patients

	Mwaungulu 2004 (5) (Malawi)	**Nunn 2008 (1) (Zambia)**	**Grimwade 2005 (2) (South Africa)**	**Kalou 2005 (6) (Côte d'Ivoire)**
Methods/design	A cohort study with a retrospective control group.	Double-blind placebo controlled randomized clinical trial.	Cohort study using historical controls.	Controlled randomized clinical trial using retrospective data from a previous study.
Population	TB patients registered in 1999 and 2000 in Karonga District, Malawi; 335 and 362 respectively, of whom 70% were HIV-positive.	Two groups of HAART-naive adults with HIV infection: patients newly diagnosed as having TB and receiving anti-TB treatment either for the first time or for retreatment after relapse; previously treated patients not receiving treatment. Lusaka, Zambia, University Teaching Hospital (UTH) chest clinic. 1003 patients were randomized: 835 (416 CPT, 419 placebo) received anti-TB treatment; 762 (376 CPT, 386 placebo) were newly diagnosed previously untreated patients and 73 (40 CPT, 33 placebo) were receiving a retreatment regimen; 168 (CPT 84 placebo) were not on treatment but had been treated in the past.	Adults treated for TB between 1998 and 2000 (control group: 2004) All adults starting treatment for TB between June 2001 and June 2002 **irrespective of HIV status** (intervention group: 1321).	HIV-1-infected patients with newly diagnosed, sputum-smear positive for *Mycobacterium tuberculosis* pulmonary infection. All patients received a standard TB regimen with or without CPT. Patients in the CPT arm were compared with those in the placebo arm at the start of treatment, and similarly were compared with the patients of both arms to each other 12 months after initiation of the treatment. Of the 44 patients (23 males, 52%) eligible for analysis in this study, 25 (56.8%) were on combined treatment of TB (CPT group) and 19 (43.2%) were on standard treatment of TB only (placebo group); 32/44 (70%) were infected with HIV-1, and 30% were dually sero-reactive to HIV-1 and HIV-2.
Intervention	CPT (960 mg OD) was given to HIV patients enrolled since January 2000. Reduced doses were given to children. Case ascertainment, follow up and care were identical in the 2 years except that in 2000 CPT was administered to HIV patients. CPT was given from the time a patient was identified as HIV-positive until 12 months after registration. Intention to treat analysis	Randomized participants in a 1:1 ratio to receive a supply of pre-labelled trial medicine (i) CPT or (ii) matching placebo; (2 tablets to be taken daily). Each CPT (400 mg sulfamethoxazole and 80 mg trimethoprim).	All adults starting TB treatment between June 2001 and June 2002 were offered CPT prophylaxis (960 mg OD for 6 months) during TB treatment irrespective of HIV status.	960 mg OD of CPT or placebo starting 1 month into standard treatment of TB.
Analysis	Intention to treat analysis	Intention to treat analysis	Intention to treat analysis	Intention to treat analysis

Table 1: Summary of studies on co-trimoxazole preventive therapy (CPT) in HIV-infected TB patients

	Mwaungulu 2004 (5) (Malawi)	Nunn 2008 (1) (Zambia)	Grimwade 2005 (2) (South Africa)	Kalou 2005 (6) (Côte d'Ivoire)
Participants	**Inclusion criteria:** patients with positive cultures, smears, biopsies for AFB. Used only HIV test data that were available <16 days after the patients was registered for anti-TB treatment. The intervention was limited to HIV-positive TB patients. **Exclusion criteria:** Pregnancy, breastfeeding, child aged <2 years, previous reactions to sulfonamide drugs.	**Inclusion criteria:** newly diagnosed, previously untreated patients with smear-positive pulmonary tuberculosis receiving anti-TB treatment (after 1 year, patients receiving a retreatment regimen were also eligible) and clinically healthy people previously treated for TB but no longer receiving any treatment. **Exclusion criteria:** WHO stage 4 HIV diseases that were unlikely to survive more than 2 weeks as well as those with a history of sulphonamide allergy and those who needed treatment with or were already receiving CPT for other indications.	**Inclusion criteria:** All adult patients with TB (aged 13 years or older) treated in the community from January 1998 to December 2000 (controls). All newly registered TB patients (September 2001 – June 2002) **Exclusion criteria:** Pregnancy, patients who declined consent to the treatment.	**Inclusion criteria:** patients who were newly diagnosed to be sputum-smear positive for pulmonary TB. Plasma specimens should be available at the beginning and at 12 months following start of therapy, patients must have been cured for TB, as determined by a smear-negative or culture-negative result, after 4 months of treatment for TB.
Follow-up	Survival was assessed at 1-2-8-12-18 months after registration as TB patient.	Total of 1012.6 person-years of follow-up. Follow-up from the time of randomization ranged from 0 to 46 months. Every 4 weeks up to 16 weeks and every 8 weeks thereafter until the close of the trial.	1 year after TB diagnosis and traced at 6 months after end of treatment.	12 months after initiation of the anti-TB treatment.
Outcomes				
Number of illness episodes and deaths avoided.	Overall case-fatality rate fell from 37% to 29%. Unchanged in the HIV-negative patients but fell in HIV-positive patients from 43% to 24%.	A total of 310 (147 CPT 163 placebo) participants died, corresponding to mortality rates of 27.3 and 34.4 per 100 person-years. In the Cox regression analysis, the HR for death (CPT:placebo) was 0.79 (95% confidence interval 0.63 to 0.99). CPT was associated with a 21% reduction in all cause mortality. The effect of CPT waned with time, possibly owing to falling adherence levels; in a per-protocol analysis based on patients who spent at least 90% of their time at risk supplied with the study medicine, the HR was 0.65 (0.45 to 0.93). The NNT to prevent one death was 141.8 (95% CI 71.7–588.7). Analysis by CD4 count on the subset of participants with data available showed no evidence of difference in benefit according to the level of immunosuppression (P>0.5, test for heterogeneity); no difference in benefit by age or sex.	Mortality at 6 months was 29% lower in the group given CPT than in the control group. The NNT to prevent one death during the period of TB treatment was 24. The benefit was seen across all types of TB but was only evident in new patients; patients being retreated had similar outcomes in both groups.	Persistently elevated levels of HIV-1 VL were documented among HIV-1-infected patients with TB despite successful treatment of TB. The increase in plasma HIV-1 VL may help to explain the high mortality observed among HIV-1- infected patients who successfully complete treatment of TB.

Table 1: Summary of studies on co-trimoxazole preventive therapy (CPT) in HIV-infected TB patients

	Mwaungulu 2004 (5) (Malawi)	Nunn 2008 (1) (Zambia)	Grimwade 2005 (2) (South Africa)	Kalou 2005 (6) (Côte d'Ivoire)
Secondary outcomes				
Morbidity/hospital admissions	NA	NA	NA	NA
Adverse events (defined as those causing cessation of the therapy or hospitalization)	NA	Suspected adverse events leading to a planned interruption of trial medicine occurred in 18 patients (12 CPT, 6 placebo); all except 6 (all CPT) resumed the trial medicine. The reactions leading to permanent discontinuation were Stevens–Johnson syndrome and anaemia, itchy rash, swollen face and lips, peripheral neuropathy, and anaemia (2 cases).	Adverse events were infrequent and minor (only 2 participants stopped treatment for this reason). Perceived adverse reactions were given as the reason for stopping prophylaxis by 23 patients but only 2 significant adverse reactions were identified. One patient developed Stevens–Johnson syndrome while still taking anti-TB treatment; this improved on cessation of both prophylaxis and anti-TB medication. A second patient (known to be HIV-positive) developed early exfoliative dermatitis at 9 months after TB diagnosis.	NA
Loss to follow up	NA	No information on 78 (37 CPT, 41 placebo) (9.3%) participants after randomization.	429 participants	No loss to follow up
Comments	Analyses including all TB patients were also performed.	Patients previously treated for TB should be excluded.	115 patients resulted HIV-positive (8.8%).	

Table 1: Summary of studies on co-trimoxazole preventive therapy (CPT) in HIV-infected TB patients

	Zachariah 2003 (Malawi) (3)	Wiktor 1999 (Ivory Coast) (4)	Chimzizi 2004 (Malawi) (7)
Methods/design	Cohort study using historical controls	Randomized double blind case-control	Cohort study using routinely collected programme data.
Population	A cohort of TB patients registered under routine programme conditions in a rural district of Malawi. A total of 1986 patients were registered in the study: 1061 (intervention) and 925 (control). Between 1 July 1999 and 30 June 2000 all TB patients were started on standardized anti-TB treatment, and offered VCT.	Between October, 1995, and April, 1998, were enrolled 771 HIV-1 and HIV-1 & HIV-2 dually seroreactive patients who had sputum-smear-positive pulmonary TB (median age 32 years [range 18–64], attending Abidjan's four largest outpatient TB treatment centres.	Two rural districts in Malawi: Thyolo (1103 pts), where VCT is offered to all TB patients and adjunctive CPT to HIV-positives, and Mulanje (1239), where no such interventions are offered.
Intervention	Patients found to be HIV-positive were offered CPT (480 mg BD), provided there were no contraindications.	**Patients were randomly assigned one daily tablet of CPT (n=386) or placebo (n=385) 1 month after the start of a standard 6-month TB regimen.**	In Thyolo District, all TB patients registered between July 1999 and June 2000 were offered VCT, and those found to be HIV-pos were given CPT (480 mg BD), provided there were no contraindications.
Analysis	Intention-to-treat	Intention-to-treat	Intention-to-treat
Participants	**Inclusion criteria:** Between 1 July 1999 and 30 June 2000, all TB patients who were registered in Thyolo district, at either the government hospital or the mission hospital, were enrolled into the VCT and adjunctive CPT treatment study (intervention group). Between 1 July 1998 and 30 June 1999, all TB patients who were registered in the same two hospitals in the district were started on the same standardized anti-TB treatment (control group). **Exclusion criteria:** Known allergies to sulfonamide drugs, pregnancy, breast-feeding until 2 months and children aged less than 2 years (because of uncertainty about HIV-serostatus).	**Inclusion criteria:** All those aged 18 years or older who lived in Abidjan, who had sputum-smear-positive TB, and who were HIV-1 seropositive or HIV-1 and HIV-2 dually seroreactive. **Exclusion criteria:** HIV-2-seropositive patients because of low mortality risk, pregnant women, patients with previously treated tuberculosis, those allergic to CPT, and those receiving CPT prophylaxis for prevention of a recurrence of toxoplasmosis.	**Inclusion criteria:** Smear positive PTB and EPTB, smear negative PTB and EPTB. Retreatment patients (Both arms), HIV positive test (intervention arm). **Exclusion criteria:** Patients were not given CPT if pregnant or allergic to CPT.
Follow-up	Until end of TB treatment	24 months	NA

Table 1: Summary of studies on co-trimoxazole preventive therapy (CPT) in HIV-infected TB patients

	Zachariah 2003 (Malawi) (3)	Wiktor 1999 (Ivory Coast) (4)	Chimzizi 2004 (Malawi) (7)
Number of illness episodes and deaths avoided.	Death was defined as a death at any time during the 8–12 months of treatment from whatever cause. The crude relative risk (RR) of death by the end of treatment in the intervention compared group with the control group was 0.78 (95% CI, 0.69–0.89; p=0.001). Adjusted for type and category of TB as well as anti-TB treatment, the RR was 0.81 (95% CI, 0.75–0.87; p= 0.001). The death rate for all registered TB patients was 4.0 per 100 person-months of follow-up in the intervention group and 5.3 in the control group, corresponding to a 25% reduction in risk of death (95% CI, 12.3–35.8). Adjusted for type and category of TB as well as anti-TB treatment, the HR was 0.76 (95% CI, 0.69–0.83). The NNT to prevent one death (by providing VCT plus CPT) during the course of anti-TB treatment was 12.5.	51 patients in the CPT group (13.8/100 person-years) and 86 in the placebo group (25.4/100 person-years) died (decrease In risk 46% [95% CI 23–62], p<0·001).	Adjusted for type and category of TB, TB treatment regimen and site of registration, the relative risks for all TB patients in Thyolo compared with those in Mulanje were: - Treatment success RR 1.23 (95%CI 1.19–1.26, p= 0.001); - Death RR 0.84 (95%CI 0.78–0.91, p=0.001); - "Other outcomes" (default, transfer out, unknown and, for smear-positive patients, failure) RR 0.27 (95%CI 0.23–0.32, p= 0.001).
Secondary outcomes			
Morbidity/hospital admissions	NA	29 patients on CPT (8.2/100 person-years) and 47 on placebo (15.0/100 person-years) were admitted to hospital at least once after randomization (decrease 43% [10–64]), p=0.02). The rate of admissions for all diseases that could potentially have been prevented by CPT (septicaemia, enteritis, chest infection, urinary-tract infection, and toxoplasmosis) was significantly lower for patients in the CPT group (2.7/100 person-years) than in the placebo group (8.7/100 person-years; HR 0.3 [0.2–0.7], p=0.001). There were significantly fewer admissions for septicaemia and enteritis in the CPT group than in the placebo group.	NA
Adverse events, defined as those causing cessation of the therapy or hospitalization	Of 693 patients on CPT, 14 (2%) had a dermatological reaction. No reactions were serious or involved mucosal membranes, and all were reversible on discontinuing treatment. All dermatological reactions occurred in the first 2 months of treatment, with 9 (64%) occurring during the first month. In 13 patients, CPT was discontinued indefinitely, and in one patient it was re-started (by mistake) without problems.	About 16 % of patients in the placebo group and 12% in the CPT group had at least one severe clinical adverse event. About 8% of the patients in each group had a severe toxic effect based on laboratory measurements. Rates of laboratory and clinical adverse events were similar in the two groups.	NA

Table 1: Summary of studies on co-trimoxazole preventive therapy (CPT) in HIV-infected TB patients

	Zachariah 2003 (Malawi) (3)	Wiktor 1999 (Ivory Coast) (4)	Chimzizi 2004 (Malawi) (7)
Loss to follow up	19 missed, 6 transferred, 3 absconded, 36 died, 53 refused VCT	A total of 984 patients were invited to participate, of whom 771 (78.4%) were enrolled. The main reasons for non-enrolment were not returning to the TB clinic (74%), transfer by the TB-clinic physicians to a non-study clinic (22%) or death before enrolment (4%).	NA
Comments	The intervention being evaluated considered the combination of CPT and VCT. The analysis is therefore not restricted to the use of CPT only. No significant benefit in smear-positive TB patients.	On April 1998, based on a review of the available results, and since it was thought no longer ethical to continue to enrol new patients, the drug safety monitoring board recommended suspension of enrolment: ALL study patients received open-label CPT Antibiotic sensitivity testing revealed that 6/7 (86%) isolates of non-typhoid salmonella were sensitive to CPT. Median CD4-cell count 317cells/L)	

BD, twice daily; CPT, co-trimoxazole preventive therapy; EPTB, extrapulmonary tuberculosis; HR, hazard ratio; NNT, number needed to treat; OD, once daily; PTB, pulmonary tuberculosis; RR, risk ratio TB, tuberculosis; VCT, voluntary counselling and testing; VL, viral load.

3. GRADE profile

The quality of evidence across a body of evidence was assessed using the GRADE approach. For purposes of systematic reviews, the GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest (*8*). The quality of a body of evidence involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The GRADE system entails an assessment of the quality of a body of evidence for each individual outcome.

The quality rating across studies has four levels: high, moderate, low or very low. Randomized trials are categorized as high-quality but can be downgraded; similarly, observational studies can be upgraded. Factors that decrease the quality of evidence include limitations in design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, or high probability of publication bias. Factors that can increase the quality level of a body of evidence include a large magnitude of effect, if all plausible confounding would reduce a demonstrated effect and if there is a dose-response gradient. The GRADE Profiler software was used to perform the GRADE analyses (GRADE pro 2008).

Given the availability of two randomized controlled trials and the unlikelihood of achieving a better quality of evidence by including the observational studies, the GRADE analyses were restricted to the two randomized controlled trials available as follows.

Table 2

Question: Should routine co-trimoxazole preventive therapy (CPT) be used in HIV-infected individuals with active TB?

Settings: High TB/HIV prevalence settings

Bibliography: Nunn A, 2008 (*1*) Wiktor SZ, 1999 (*4*)

Routine CPT prophylaxis for HIV-infected individuals with active TB

Patient or population: HIV-infected individuals with active TB

Settings: High TB/HIV prevalence settings

Intervention: Routine CPT prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Routine CPT prophylaxis				
Mortality Medical record Follow-up: 332–538 patient-years	**Study population**		**RR 0.70** (0.6 to 0.83)	1711 (2 studies)	++++ **high**[1]	
	309 per 1000	**216 per 1000** (185 to 256)				
	Medium risk population					
	300 per 1000	**210 per 1000** (180 to 249)				
Morbidity/hospital admission Medical and hospital record Follow-up: 332–366 patient-years	**Study population**		**HR 0.54** (0.39 to 0.74)	698 (1 study)	+++- **moderate**[2]	
	259 per 1000	**140 per 1000** (101 to 192)				
Adverse events Medical record Follow-up: 332–538 patient-years	**58 per 1000**	**46 per 1000** (31 to 67)	**RR 0.79** (0.54 to 1.15)	1599 (2 studies)	+++- **moderate**[3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI, confidence interval; **RR**, risk ratio; **HR**, hazard ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Patients were not on HAART and this could be considered as a significant difference between the trial subjects and the patients for whom the recommendation is intended; however, this is likely to be a minor issue therefore the studies were not downgraded.

2 Only one study available.

3 Wide CI.

Table 3a

Question: Should routine co-trimoxazole preventive therapy (CPT) be used in HIV-infected individuals with active TB and CD4 count <200 cells/mm^3?

Settings: High TB/HIV prevalence settings

Bibliography: Wiktor SZ, 1999 (*4*)

Routine CPT prophylaxis for HIV infected individuals with active TB and CD4 count <200 cells/mm^3

Patient or population: HIV infected individuals with active TB and CD4 count <200 cells/mm^3

Settings: High TB/HIV prevalence settings

Intervention: Routine CPT prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Routine CPT prophylaxis				
Mortality Medical record Follow-up: 76–99 patient-years	**Study population**		**RR 0.47** (0.33 to 0.66)	175 (1 study)	++-- **low**[1,2]	
	645 per 1000	**303 per 1000** (213 to 426)				
	Low risk population					
	200 per 1000	**94 per 1000** (66 to 132)				
	High risk population					
	700 per 1000	**329 per 1000** (231 to 462)				
Hospital admission Medical and hospital record Follow-up: 67–94 patient-years	**Study population**		**RR 0.44** (0.26 to 0.75)	161 (1 study)	++-- **low**[1,2]	
	403 per 1000	**177 per 1000** (105 to 302)				
	Medium risk population					
	500 per 1000	**220 per 1000** (130 to 375)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI, confidence interval; **RR**, risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Only one study available.

2 Small sample size and wide CI.

Table 3b

Question: Should routine co-trimoxazole preventive therapy (CPT) be used in HIV-infected individuals with active TB and CD4 count >200 cells/mm^3?

Settings: High TB/HIV prevalence settings

Bibliography: Wiktor SZ, 1999 (*4*)

Routine CPT prophylaxis for HIV-infected individuals with active TB and CD4 count >200 cells/mm^3

Patient or population: HIV-infected individuals with active TB and CD4 count >200 cells/mm^3

Settings: High TB/HIV prevalence settings

Intervention: Routine CPT prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Routine CPT prophylaxis				
Mortality Medical record Follow-up: 251 patient-years	**Study population**		**RR 0.48 (0.26 to 0.89)**	502 (1 study)	++-- **low**[1,2]	
	116 per 1000	**56 per 1000** (30 to 103)				
	Low risk population					
	100 per 1000	**48 per 1000** (26 to 89)				
	High risk population					
	400 per 1000	**192 per 1000** (104 to 356)				
Hospital admission Medical and hospital record Follow-up: 241–244 patient-years	**Study population**		**RR 0.60 (0.27 to 1.35)**	485 (1 study)	++-- **low**[1,2]	
	62 per 1000	**37 per 1000** (17 to 84)				
	Medium risk population					
	200 per 1000	**120 per 1000** (54 to 270)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI, confidence interval; **RR**, risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Only one study available.

2 Small sample size and wide CI.

4. Risk and benefits assessment

Recommendation: Routine co-trimoxazole preventive therapy (CPT) should be administered in all HIV-infected patients with active TB disease regardless of their CD4 count

Population: HIV-infected patients with active TB disease irrespective of their CD4 count

Intervention: Standard routine CPT administration

Factor	Decision	Explanation
Quality of evidence	High	The reduction in mortality is supported by the HIGH quality of the evidence. The intervention shows decrease in morbidity and hospital admission (LOW quality of the evidence) with no significant increase in adverse events (MODERATE quality of the evidence) Lack of specific evidence in HIV infected patients on ART
Benefits or desired effects	Strong (benefits outweigh risks)	Reduction in mortality Reduction in morbidity (bacterial infection, malaria, etc.) including among HIV-uninfected household members of people living with HIV receiving CPT (but not exclusively HIV-infected TB patients)
Risks or undesired effects		Additional drug-related adverse events Resistance rates to CPT among common pathogens may increase, although this was not the case on diarrhoeal pathogens in Uganda and on falciparum parasites in Mali (studies conducted among people living with HIV receiving ART – not exclusively HIV-infected TB patients – and their household members)
Values and preferences	Strong	Improve quality of HIV care Prevention of life-threatening opportunistic infections Health-care workers would probably prefer standard policy regarding CPT irrespective of antituberculosis treatment
Costs	Strong	CPT is inexpensive and available Unlikely to increase cost significantly Avoiding additional hospitalization: potentially cost-saving
Feasibility	Strong	Routine CPT provision is part of HIV general care Continuation of standard provision is very feasible Downside is that CPT is a common antibiotic for people with and without HIV and it is often difficult to maintain regular supply for those in need.
Strength of recommendation **Strong**		

5. References

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World Health Organization

For further information contact:

World Health Organization
20, Avenue Appia CH-1211 Geneva 27 Switzerland
Stop TB Department
E-mail: tbdocs@who.int
Web site: www.who.int/tb

Department of HIV/AIDS
Email: hiv-aids@who.int
Web site: www.who.int/hiv

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