

WHO/TB/98.255
UNAIDS/98.34
Distr: GENERAL
Original: English

*Policy Statement on Preventive
Therapy against Tuberculosis in
People Living with HIV*

*Report of a Meeting held in Geneva
18 – 20 February 1998*

**World Health Organization
Global Tuberculosis Programme
and
UNAIDS**



UNAIDS
UNICEF • UNDP • UNFPA
UNESCO • WHO • WORLD BANK



**WORLD HEALTH
ORGANIZATION**



WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

DISTR. : GENERAL(E)
WHO/TB/98.255
UNAIDS/98.34
Original: English

*Policy Statement on Preventive Therapy against
Tuberculosis in People Living with HIV*

*Report of a Meeting held in Geneva
18 - 20 February 1998*

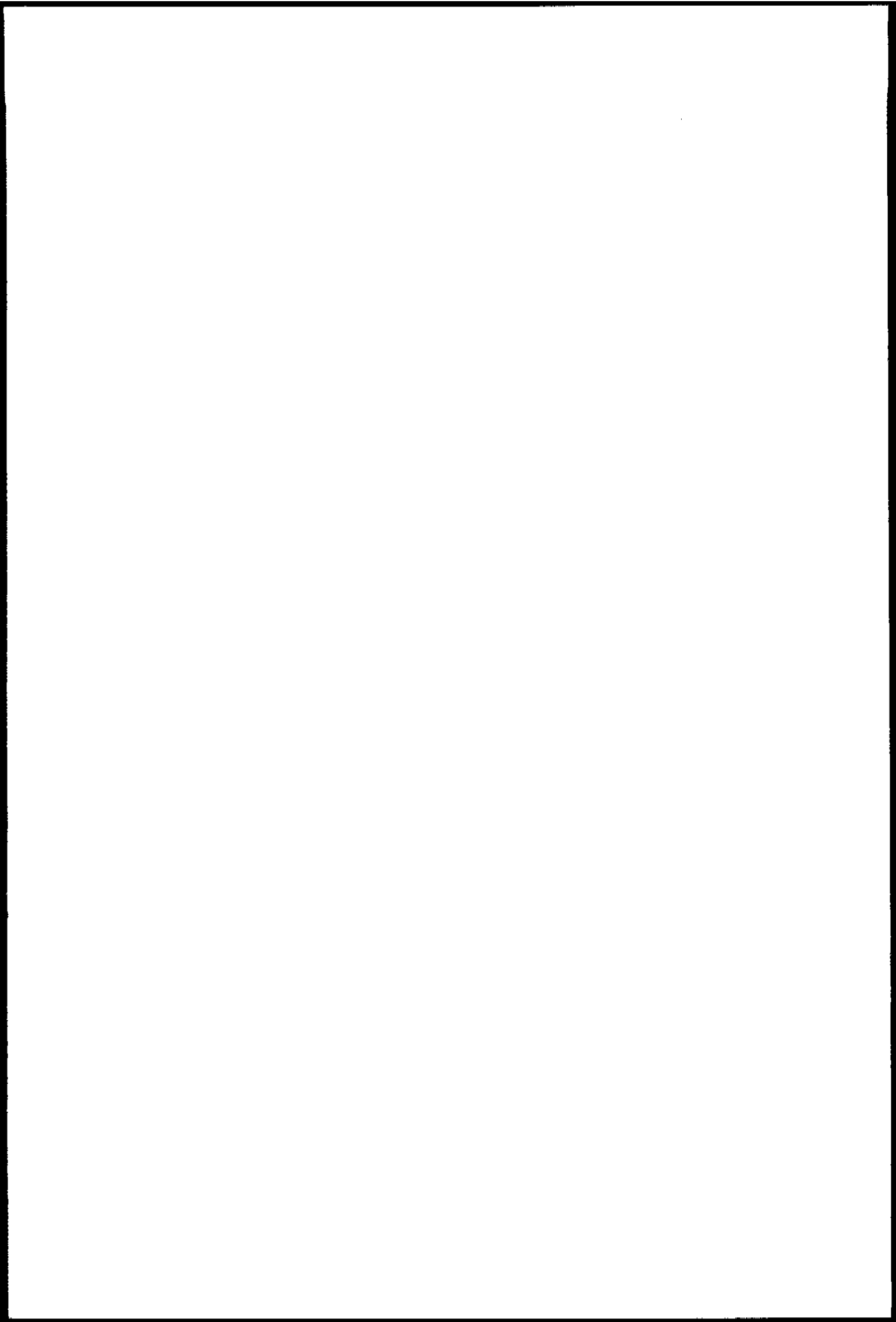
**World Health Organization
Global Tuberculosis Programme
and
UNAIDS**

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced and translated, in part or in whole, but not for sale nor for use in conjunction with commercial purposes.

The views expressed in documents by named authors are solely the responsibility of those authors.

Ce document n'est pas une publication officielle de l'Organisation mondiale de la Santé (OMS) et tous les droits y afférents sont réservés par l'Organisation. S'il peut être commenté, résumé, reproduit ou traduit, partiellement ou en totalité, il ne saurait cependant l'être pour la vente ou à des fins commerciales.

Les opinions exprimées dans les documents par des auteurs cités nommément n'engagent que lesdits auteurs.



Policy statement on preventive therapy against tuberculosis in people living with HIV

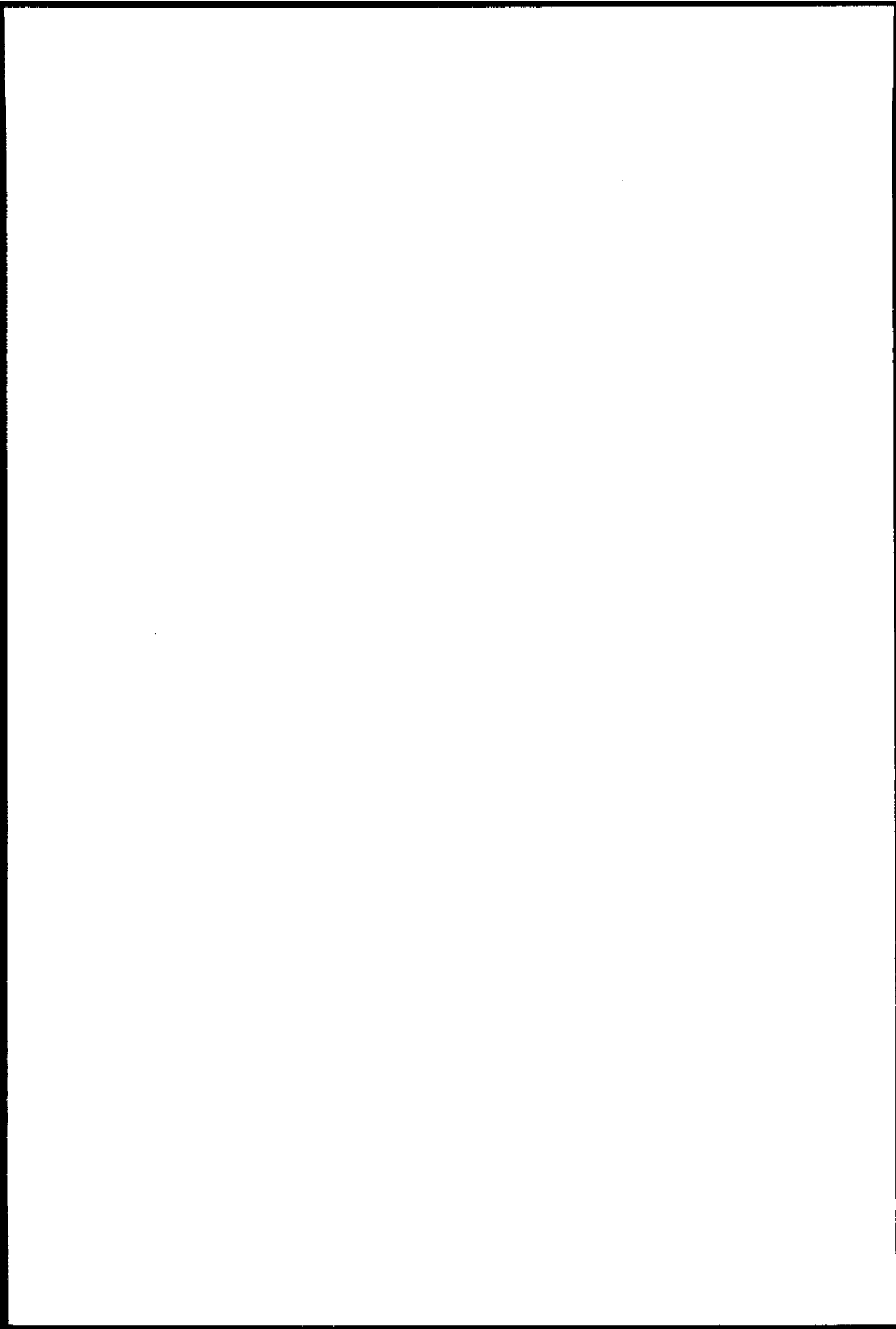
Author

Peter Godfrey-Faussett

Acknowledgements

The Global Tuberculosis Programme (GTB) and UNAIDS acknowledge the following individuals who contributed to the writing of the report : David Cohn and Gavin Churchyard. Those individuals who participated in the meeting and gave additional constructive comments on earlier drafts include : K. De Cock, D.Kibuga, R. O'Brien, H.Rieder, C. Whalen and J.Ngamvithayapong. The document was also discussed and endorsed by the Technical, Research and Advisory Committee of GTB.

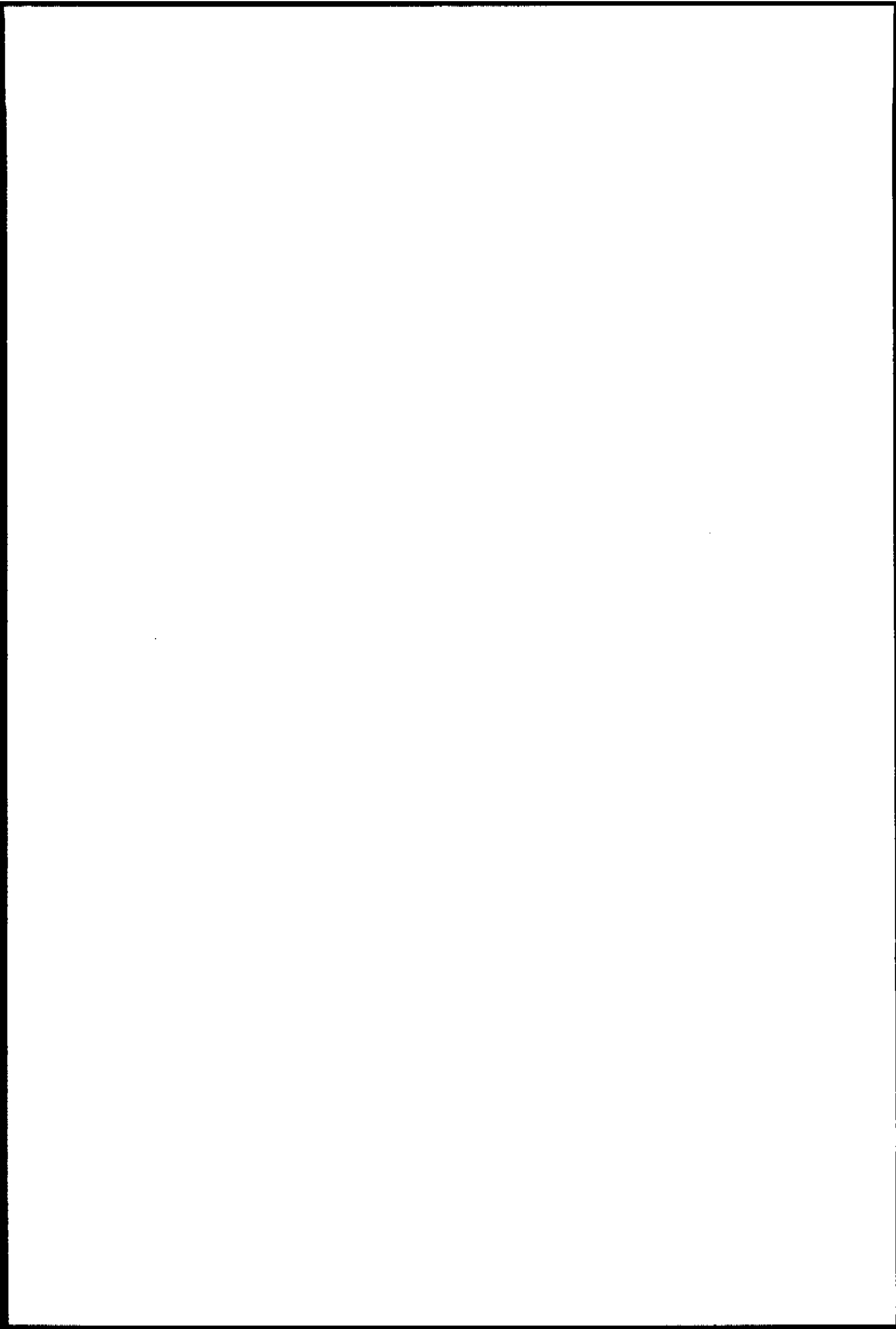
The author thanks Jeanette Dadzie for her assistance in the production of the document



Policy statement on preventive therapy against tuberculosis in people living with HIV

Contents

Policy statement on preventive therapy against tuberculosis in people living with HIV	3
Technical Annex	7
Introduction	7
Efficacy of preventive therapy in HIV infected individuals	8
Feasibility of preventive therapy	13
Cost-efficacy and cost-benefit	14
Current voluntary counselling and testing initiatives	16
Potential impact of preventive therapy	16
Delivery of preventive therapy services	17
Drug regimens	17
Conclusions	18
References	20
List of participants	23



Policy statement on preventive therapy against tuberculosis in people living with HIV

Preamble

Preventive therapy (PT) against tuberculosis is the use of one or more anti-tuberculosis drugs given to individuals with latent infection with *Mycobacterium tuberculosis* in order to prevent the progression to active disease. HIV is the most powerful known risk factor for progression from latent infection with *M. tuberculosis* to active disease, and this is the major cause of the large increase over the last decade in the incidence of tuberculosis in populations with a high prevalence of HIV infection. Several large randomised controlled trials have now demonstrated that PT is effective in preventing TB in individuals dually infected with HIV and *M. tuberculosis*. However, studies of the feasibility of PT demonstrate that the process required to target appropriate individuals, to exclude active tuberculosis, to deliver PT and to achieve adherence is complex and inefficient.

In February 1998, WHO and UNAIDS convened a meeting to review the data available and to make recommendations to governments that would serve to update the recommendations published by WHO and IUATLD in 1993. This document presents the recommendations arising from the meeting. More detailed reviews of the data leading to these recommendations are presented as an annex.

The following prerequisites are identified which should be in place before a PT service is considered:

- Adequate capacity for HIV counselling
- Sufficient trained health care staff
- Linkage between HIV care and TB control services
- TB treatment services that have a high probability of curing cases of TB identified through the PT service (eg less than 10% default or failure at the end of treatment)

In settings meeting these standards,

WHO and UNAIDS recommend to governments that: -

- 1) Preventive therapy should be part of a package of care for people living with HIV/AIDS.
- 2) Preventive therapy should only be used in settings where it is possible to exclude active tuberculosis cases and to ensure appropriate monitoring and follow up.
- 3) Information about tuberculosis including preventive therapy should be made available to people with HIV.
- 4) Preventive therapy should be provided from within settings that include established voluntary counselling and testing (VCT) services for HIV.

- 5) The priority for TB control programmes continues to be the detection and cure of infectious tuberculosis cases.
- 6) The procurement and supply of tuberculosis drugs must be regulated by national authorities, in order to prevent the development of drug resistance.

Implementation of a PT service needs to occur in the context of integrated care, with benefits to TB control, HIV care and public health programs. In many of the countries most affected by the dual epidemics of HIV and TB, the TB programme is already over-stretched. Although the responsibility for funding and running a PT service may be taken by government health services or non-governmental HIV care organisations, active participation of TB programmes will be necessary particularly for training, diagnosis of tuberculosis, treatment of tuberculosis cases and drug logistics and procurement. PT services will therefore need to demonstrate that their involvement in finding cases of tuberculosis and supervision of patients on treatment balances the participation of the TB programme, to their mutual benefit.

Individuals seeking voluntary HIV testing should be offered pre-test counselling. Those who choose to be tested should be offered quality assured HIV testing and post-test counselling.

Different models of delivery will be appropriate in different settings and may use capacity from governmental clinics, stand-alone VCT sites, NGOs, maternal health services etc.. However, among the range of services provided to those found to be living with HIV, the following steps should be included in the delivery of PT:

Those who have a positive HIV test should receive:

1. counselling on tuberculosis
2. screening for active tuberculosis
3. targeting of those most likely to benefit from PT
4. provision of preventive therapy to those without active tuberculosis
5. monitoring for adherence and toxicity
6. evaluation of outcome

1. Counselling on tuberculosis

People living with HIV are at risk of developing TB. They should be given health education and encouraged to seek early diagnosis and treatment of cough and other symptoms suggestive of TB.

2. Screening for active tuberculosis.

PT is inadequate treatment for active TB and could lead to the development of drug resistance. Active TB should therefore be excluded before PT is started. The setting of different PT services and the available capacity within government health services will determine at what stage

patients need to be referred. All people attending for HIV counselling and testing should be asked whether they have a cough, and those that do should be screened for TB. Those found to have TB should be registered and treated by the TB control programme.

While it is recognised that most people with active TB will have symptoms, until the validity of different screening tools or algorithms is established, it is recommended that a chest radiograph is examined from every individual before considering PT.

3. Targeting of those most likely to benefit.

PT is recommended for PPD+ HIV-infected individuals who do not have active tuberculosis. In some settings it may not be feasible to perform PPD testing. Under these circumstances the following individuals may still be considered for preventive therapy if they are infected with HIV:

- Those living in populations with a high prevalence of tuberculous infection (estimated to be >30%)
- Health care workers
- Household contacts of TB patients
- Prisoners
- Miners
- Other selected groups at high risk of acquisition or transmission of TB

4. Provision of PT to those without active TB

Isoniazid is the recommended drug. 5mg/kg (max. 300mg) may be given as daily, self-administered therapy for six months. Individuals should be seen monthly and given only one month supply of medication at each visit.

5. Monitoring for adherence and toxicity

Patients should be monitored at the routine visits for adherence with treatment, drug toxicity, and signs or symptoms of active tuberculosis. Patients who interrupt therapy should be counselled about the reasons for stopping. PT should only be restarted if the obstacles to adherence have been removed. The aim is to provide at least six months of isoniazid therapy during a one year period. Pill counts and self-report may be useful in assessing adherence.

Clients with symptoms of tuberculosis or toxicity to medication should be evaluated immediately. Preventive therapy should not be continued if the patient develops signs or symptoms of tuberculosis. These suspected cases must be properly evaluated for active tuberculosis and referred to the National TB Program for registration and treatment.

Although biochemical monitoring of liver enzymes for hepatitis is not routinely recommended, patients should be carefully educated about the symptoms of hepatitis and instructed to discontinue the drug promptly should these occur.

6. Evaluation of outcome

Programs or centres that offer PT should assess the effectiveness of PT regularly. This assessment should include attendance at scheduled appointments, adherence (number of persons started on preventive therapy and number completed), toxicity and withdrawals from therapy due to toxicity, number of suspected TB cases in screening and monitoring of therapy. Individual records should be maintained to document use of PT. Individual information will be aggregated for regular reports, which may be used by the TB programme to estimate future drug requirements.

Technical Annex from Preventive Therapy Meeting held in Geneva 18-20 February

Introduction:

HIV is recognised to be the strongest risk factor for the progression of latent infection to active TB. In countries with severe HIV epidemics, there has been a dramatic rise in notification rates for TB. The DOTS strategy of TB control is based on passive case-finding through microscopic examination of sputum from those presenting to a diagnostic centre with a cough for more than three weeks followed by active case-finding with supervision of the intensive phase and efficient monitoring of the outcome of treatment. Such a strategy is capable of curing the large majority of cases and preventing the development of chronic cases who may continue to spread infection in the community and who have a much higher chance of having drug resistant disease. Nonetheless, even when the DOTS strategy is well applied, ongoing transmission of infection occurs before patients present to the diagnostic centres.

Preventive therapy is the use of isoniazid or other anti-tuberculous drugs aiming to sterilise latent infection with *Mycobacterium tuberculosis* and thus prevent progression to active disease. Prior to the HIV epidemic, its use in countries with a high prevalence of TB was limited to childhood contacts of active cases since these children have a higher risk of progression to disseminated and severe forms of disease.

Several studies have recently been completed considering the efficacy, feasibility and cost-efficacy of preventive therapy in HIV-infected people in countries with a high prevalence of TB. It is therefore appropriate to consider the role PT should have as an addition to DOTS in countries burdened by the dual epidemic of HIV and TB. In February 1998, the Global Tuberculosis Programme of the WHO and UNAIDS, convened a meeting whose aim was to develop a set of guidelines for policy makers. This document forms a technical annex to those guidelines and sets out the process by which the guidelines were developed, as well as the technical information on which they are based.

The meeting brought together around 50 people (listed in annex 2), drawn from four groups:

1. Technical experts, from TB, HIV and health economics backgrounds
2. Potential consumers, PLWHs and their advocates, HIV care organisations
3. Policy makers, involved in health planning and commissioning of services
4. Donor agencies involved in health financing, particular those involved with HIV and TB

The first day was spent reviewing the current state of knowledge with regard to the interactions between TB and HIV at the biomedical and programmatic level; strategies for TB control; approaches to HIV care; experience with voluntary HIV counselling and testing; efficacy, feasibility and cost-efficacy of preventive therapy.

For the next two days the participants and secretariat from WHO and UNAIDS divided into four working groups. The working groups addressed overlapping areas of debate and so all four groups reconvened at intervals to present the content of their deliberations and to gain input from the other groups. The groups' draft recommendations were then collated by a writing committee and presented to the meeting participants before its close.

This document summarises the evidence presented and discussed and serves as a technical annex to support the policy statement.

Efficacy of PT in HIV infected individuals.

Table 1 summarises data from various studies that have measured the incidence rate of TB in different populations of HIV infected individuals.

Some studies have included subjects whatever the result of PPD testing, while others have only included PPD +ve or anergic subjects. In some studies the rates in all PPD-ves can be estimated by combining the anergic group with the other PPD -ve subjects.

Differences in rates reflect inclusion criteria, case definitions, and background risk of infection with *Mycobacterium tuberculosis*. Rates are consistently higher in PPD+ groups and are higher in anergic subjects than non-anergic, PPD -ve subjects. The age-groups recruited included those known to be at highest risk of developing active TB, so these rates cannot be directly compared with incidence rates that use total population as a denominator.

Table 1
Incidence of TB among people living with HIV

Study ref	Country/Population	TB rates % per year (Number in sample)			
		Total	PPD+	PPD-	Anergic
<i>Studies from USA and Europe</i>					
Selwyn 89	USA IDU	2.1 (215)	7.9 (49)	0.3 (166)	
Selwyn 92	USA IDU		9.7 (25)		6.6 (68)
Gordin 97	USA 60% IDU				0.9 (257)
Moreno 93	Spain IDU	9.6 (290)	10.4 (76)	6 (214)	8.1 (90)
Moreno 93	Spain nonIDU	0 (57)	0 (8)	0 (49)	0 (22)
Guelar 93	Spain 60% IDU	2.8 (768)	16.2 (26)	2.4 (742)	2.6 (235)
Antonucci 95	Italy 70% IDU	2.2 (5520)	4.5 (207)	2.1 (5313)	2.9 (1687)
<i>Studies from Latin America</i>					
Pape 93	Haiti	7.5 (70)	10.0 (25)	5.7 (35)	
Valdespino 93	Mexico		5 (69)		
<i>Studies from Africa</i>					
Braun 91	Zaire Women	3.1 (249)			
Allen 92	Rwanda Women	2.4 (401)	5.5 (73)	2.1 (211)	
Wadhaven 92	Zambia	5.3 (246)			
Hawken 97	Kenya	3.9 (342)	8.0 (69)	2.7 (224)	
Whalen 97	Uganda		3.4 (465)		3.1 (323)
Mwinda 98	Zambia	4.9 (350)	9.2 (60)	3.1 (166)	

In high TB prevalence countries, between 2.4 and 7.5% of HIV infected adults may develop active TB each year. In those with a positive PPD test, the rate rises to between 3.4 and 10% per year.

Efficacy of isoniazid preventive therapy

Studies of efficacy of isoniazid preventive therapy compared to placebo are summarised in table 2. The table includes trials using 6-12 months of isoniazid given daily or twice weekly. Two meta-analyses that have been performed are also included.

Table 2
Efficacy of isoniazid preventive therapy

ID	Study ref	Country	Follow Up			Rate ratios (RR) or Odds ratios (OR) for INH compared to no INH [95% CI]		
			Inclusion	Median	PYRs	PPD+	Anergic or PPD -	Total
<i>Non-randomised comparisons</i>								
1	Selwyn 89	USA IDU	PPD+	1.8	390			
2	Guelar 93	Spain 60% IDU	PPD+	1.2	159	RR 0.55		
<i>Randomised controlled trials</i>								
3	Pape 93	Haiti	All	2.8	329	OR 0.17	OR 0.68	
4	Valdespino 93	Mexico	PPD+	0.3	43			
5	Wadhaven 93	Zambia	All	1.7	934			RR 0.4
6	Hawken 97	Kenya	All	1.8	1178	RR 0.6	RR 1.2	RR 1
7	Whalen 97	Uganda	PPD+ and anergic	1.1	1943	RR 0.32	RR 0.83	
8	Gordin 97	USA 60% IDU	Anergic	2.8	1417		RR 0.48	
9	Mwinga 98	Zambia	All	1.8	1631	RR 0.25	RR 0.86	RR 0.59
10	Hanvanich 98	Thailand	Anergic	Ongoing				
11	Berenger 98	Spain	Anergic	Ongoing				
<i>Meta-analyses</i>								
		ID of trials included						
	Wilkinson 97	3,6				OR 0.46 [0.2-1.07]	OR 1.02 [0.49-2.13]	OR 0.86 [0.51-1.44]
	Bucher 98	3,4,5,6,7,8				RR 0.41 [0.24-0.71]	RR 0.84 [0.52-1.38]	RR 0.58 [0.39-0.87]

All studies found a lower rate of TB in those subjects with a positive PPD test who took isoniazid compared to those who took placebo. In one study (Hawken 97) the effect was not statistically significant. The first meta-analysis (Wilkinson97) estimated an odds ratio of 0.46 with a 95% confidence interval from 0.2 to 1.07. With the addition of further studies, the second meta-analysis (Bucher 98) estimated a rate ratio of 0.41 (95% CI 0.24-0.71) and the final study that included PPD + subjects (Mwinga 98) will also shift the estimate of efficacy slightly more in favour of isoniazid.

There can therefore no longer be any doubt that treatment of PPD +ve individuals living in a setting with a high prevalence of TB with isoniazid will reduce the risk of developing active TB in the short term to around 40% of what it would have been without such treatment.

In subjects with a negative PPD test, efficacy remains unproven. Some studies have included all such subjects while others have only recruited those with demonstrated anergy to other common antigens. Gordin 97 found few cases of active TB in a large study of anergic subjects in the US (see table 1), so that there is a wide confidence interval around the estimated efficacy that includes no effect. In African studies, rates were higher in anergic subjects or those with negative PPD tests, but none has demonstrated a statistically significant effect, and the Bucher 98 meta-analysis also failed to demonstrate a statistically significant effect. The addition of the final study will tend to narrow the confidence interval around the estimated rate ratio of 0.84.

If PPD testing is unavailable or impractical, what is the estimated efficacy of isoniazid preventive therapy? Some studies included all subjects regardless of PPD result. When these trials are combined in the most recent meta-analysis, isoniazid is found to be significantly better than placebo with a rate ratio of 0.58 (95% CI 0.39 to 0.87). The estimated effect in the remaining trial is very similar so that the CI will be narrower but the final estimate unchanged.

It is therefore possible to state that treatment of HIV +ve individuals, in whom a PPD skin test cannot be performed, living in a setting with a high prevalence of TB with isoniazid will reduce the risk of developing active TB in the short term to around 60% of what it would have been without such treatment.

Mwinga 98's study also suggests that there may be tools other than a PPD skin test that may predict those most likely to benefit from preventive therapy. In that study isoniazid was associated with statistically significant protection (Rate ratio 0.28; 95% CI 0.11-0.70) in subjects who had a lymphocyte count of $> 2 \times 10^9 / l$.

Comparisons of isoniazid with other regimens.

Several studies have included regimens other than isoniazid, either as direct comparisons with isoniazid or as comparisons with a placebo arm. They are summarised in table 3.

Table 3
Studies of rifampicin containing regimens

Study ref	Country	Regimens used	Comments
Whalen 97	Uganda	3RH, 3RHZ, 6H placebo	Side effects higher with 3 drugs
Mwinga 98	Zambia	3R ₂ Z ₂ , 6H ₂ , placebo	H tends to be better than RZ
Halsey 98	Haiti	3R ₂ Z ₂ , 6H ₂	H better in first months
Gordin 98	US, Mexico, Brazil,	2RZ, 12H	Equivalent
Hanvanich 98	Thailand	4RH, 12H	Equivalent

None of these studies was designed to be powerful enough to show that rifampicin containing regimens were better than isoniazid alone, they were either comparing the rifampicin arm directly to placebo or were aiming to demonstrate equivalence. Despite animal studies suggesting that combining rifampicin and pyrazinamide led to maximum efficacy, none of the studies has demonstrated that any of the combinations studied is significantly better than isoniazid. The tendency is for isoniazid to be slightly better, raising the possibility that the longer duration of therapy may provide additional benefit.

Duration of therapy

Studies presented to date, do not allow the duration of efficacy to be quantified. Mwinga 98 noted that beyond 18 months of follow up it was no longer possible to demonstrate an effect of isoniazid. However, the small number of events limited the power of the study at that stage.

Halsey 98 showed that in the first ten months of their study, six months of isoniazid was significantly better than two months of rifampicin and pyrazinamide but that later in the study, there was no detectable difference. No cases were observed while subjects were on treatment.

Further studies will be needed to quantify the benefits and risks of continuing preventive therapy or giving repeated courses. Without better data on the longer-term effects of six or twelve months of isoniazid, it is also difficult to estimate cost-benefit ratios.

Effect of PT on mortality

The studies presented have not been designed to demonstrate an effect on mortality. The combined estimate provided by the largest meta-analysis shows a modest reduction in death rates in those subjects with a positive tuberculin skin test who took isoniazid rather than placebo (RR=0.68 95%CI 0.48 – 0.97). No effect was demonstrated in those with a negative tuberculin test and the overall estimate for all subjects in the trials did not differ from unity significantly.

The Ugandan efficacy study (Whalen et al. 1997) also showed a significant risk difference for mortality between the active and placebo arms (1.9 deaths per 100 person-years in the 3RH arm).

A model that incorporates HIV disease progression and stratified risks of developing TB has been developed (Sawert 98) and used to predict the impact of PT on life expectancy in an HIV positive cohort. Predicted increase in survival in those given PT was 3-5 months in those with a positive tuberculin skin test and up to 1 month in those with anergy.

Although the individual benefits may be rather small, widespread implementation of PT would have some impact on mortality.

Feasibility of preventive therapy

Although preventive therapy has been shown to be effective in clinical trials, the feasibility of providing it in a programme setting in developing countries is less clear. Delivery of preventive therapy requires several steps to be taken.

1. Identification of HIV positive subjects
2. Screening to exclude active tuberculosis
3. Screening to target those most likely to be infected with *M.tuberculosis*
4. Provision of drugs
5. Adherence to therapy

Data on the numbers of clients dropping out at each stage of the process were presented from completed and ongoing studies in Uganda, Thailand and Italy. Additional studies from Zambia and Thailand have studied efficacy and adherence, but have reported and discussed drop out rates. Table 4 summarises the data.

Table 4
Proportion of subjects dropping out of PT service in feasibility studies

<i>Feasibility studies in countries with high TB prevalence</i>					
		Seroprevalence in study population (%)	% of HIV +ve subjects entering PT process	% of those entering the process who started PT	% adherence
Aisu 95	Uganda 1	23	15	30	62
Aisu 98	Uganda 2	100	51	38	70
Chawalit 98	Thailand	26	95	43	74
<i>Feasibility studies in countries with low TB prevalence</i>					
Antonucci 97	Italy	100	100	2.4	
<i>Other studies that have reported on feasibility</i>					
Ngamvitha yapong 97	Thailand	100	100	89	74
Godfrey- Faussett 95	Zambia	63	62	83	

In Italy, the number of people actually starting preventive therapy was very low, largely because of the small number who had a positive PPD skin test, but also because 29% of those eligible had contraindications to isoniazid and 28% of those offered preventive therapy refused it.

In the first study in Uganda, only 15% of those who had a positive HIV test were screened by the physician, who was responsible for considering whether or not preventive therapy could be started. Once they had been seen by the physician, 30% ended up on therapy. The second

Ugandan study is still ongoing. Learning from the lessons of the first study, recruitment starts when HIV positive individuals express interest in receiving preventive therapy. 38% of such individuals progress through the screening process while 41% drop out because of their own choice rather than through exclusion. The remaining 21% are excluded because of advanced HIV disease (5%), pulmonary symptoms (11%), active TB cases (1%) or an abnormal chest radiograph (1%) or other reasons.

The second Ugandan study is also addressing the need for screening potential clients by radiography. Around 5% of clients who have already been classified as "asymptomatic" are found to have abnormal chest radiographs. The numbers are still too small to state what proportion of these abnormalities were due to TB but they include two cases of asymptomatic pleural effusion. Until the validity of different screening algorithms is assessed and the risk of giving PT to individuals with active TB can be quantified, it is recommended that all people considered for PT should have a chest radiograph examined before starting treatment.

In Northern Thailand, in an ongoing study, there are five HIV counselling and testing sites involved. HIV seroprevalence varies between 17 and 43% and in four of the sites all seropositive subjects were evaluated for preventive therapy. The proportion of those evaluated that start therapy varies between 30 and 66%.

Adherence to treatment has been between 60% and 80% in these feasibility studies, which is similar to that found in the clinical trials which were analysed on an intention to treat basis, so that the estimates of efficacy quoted above should be attainable in less controlled settings.

In order to maximise the utility of preventive therapy, attention must be paid to the selection of potential recipients and to their flow through the screening and delivery system.

Cost-efficacy and cost-benefit

The meeting highlighted the limited number of studies of cost-efficacy and cost-benefit of PT that have been carried out. Since the effect of PT on life expectancy is small, cost-effectiveness analyses using incremental costs per incremental year of life saved will be very sensitive to the calculation of costs. The decisions as to which costs and which benefits to include and whether to use marginal or average costs have to be made taking into account whether implementation would result in changes in the infrastructure and staff needed or simply the additional diagnostic supplies and drugs. Similarly, counselling and testing subjects for HIV in order to offer them PT will clearly be more expensive than offering a service to those already known to be HIV positive.

Table 5 shows estimates for different scenarios of the number of subjects who would need to be screened and treated in order to prevent a single case of active TB. The scenarios all assume that clients would only be referred to the PT service if they were known to be HIV positive and wished to consider PT. The first scenarios assume that a tuberculin skin test would be performed and only the 25-35% found positive would enter the next step. The second step would be to rule out active tuberculosis, using a chest radiograph and clinical examination. Using the estimates

provided by the feasibility and efficacy studies outlined above, between 19 and 70 clients would need to be screened with tuberculin testing to prevent one new case of TB developing. However, the number who would actually be given PT would be very much smaller (4-7) since most clients would drop out, either because of the screening procedures or for other reasons (as seen in all the feasibility studies). The costs would therefore be for screening 19-70 people and for supervising treatment for 4-7 people. The benefits would be the direct savings of the costs of treating one case of active TB as well as the additional savings of any secondary cases that would have arisen through transmission before the index was adequately treated.

Marginal costs per TB case in middle and low-income countries are around \$100. Assuming that each active case leads to at least one other case that requires treatment, a benefit of around \$200 might be obtained by treating 4-7 tuberculin skin test positive subjects with PT. Average costs are considerably higher, so a larger scale PT service would actually lead to a significantly greater saving through reduction in the number of staff or capital costs.

There would also be a benefit of earlier treatment of cases of active TB found during the screening procedures, which is not included in these estimates.

In the second set of scenarios, the screening criteria are less stringent and subjects are treated provided they do not have active TB, irrespective of tuberculin skin test results. The efficacy is lower and the proportion expected to develop TB is lower. The number needed to be screened to prevent one new case of TB developing is rather similar to the first set of scenarios (15-78) but a larger number of clients would actually be treated so that costs would be higher.

Table 5
Estimated proportions passing through a PT service to prevent one index case of TB

Screening strategy	Proportion eligible (screen1) A	Proportion eligible (screen2) B	Feasibility study results C	Efficacy study results D	Proportion expected to develop TB in absence of PT E	Estimated number needed to screen to prevent one index case $1/(A \times B \times C \times D \times E)$	Estimated number needed to treat to prevent one index case $1/(D \times E)$
1. PPD 2. CXR	0.25	0.85	0.45	0.5	0.3	70	7
	0.3	0.9	0.55	0.55	0.35	35	5
	0.35	0.95	0.65	0.6	0.4	19	4
1. CXR	0.85		0.3	0.25	0.2	78	20
	0.9		0.4	0.3	0.3	31	11
	0.95		0.5	0.35	0.4	15	7

Current VCT initiatives

While PT may provide a cost-effective intervention for those known to be HIV positive, the great majority of people living with HIV infection are unaware of their status. The costs of voluntary counselling and testing services (estimated at around \$15-\$25 per client) and the fact that most people tested will be seronegative and thus not eligible for PT, mean that establishing VCT specifically to deliver PT will not be a cost-effective approach. The meeting therefore also considered the future of VCT services in middle and low-income countries.

Voluntary HIV testing accompanied by counselling has a place within a comprehensive range of measures for HIV/AIDS prevention care and support. VCT services are currently offered through government outpatient and STD clinics; specialised VCT centres; maternal and child health clinics; HIV support and care organisations and through outreach or mobile services. Demand for VCT services is increasing, particularly as interventions such as treatment to interrupt mother to child transmission become available. AIC in Uganda has provided VCT to over 350,000 people since 1990 and Espoir in Cote d'Ivoire saw 45,000 clients and tested 25,000 in 1993-97. There is at least one Anonymous clinic in each of the 73 Thai provinces.

VCT provides an entry point not only for PT services, but also for an extended range of support, care and prevention activities. As further interventions for PLWHs are defined, the demand for VCT is likely to rise. Examples include mother to child transmission and cotrimoxazole prophylaxis.

Preliminary data from a randomised trial of VCT compared to health information alone show greater behavioural changes in those given VCT than those given information alone and extrapolations from these data suggest that VCT could be as cost-effective an intervention for HIV prevention as syndromic management of STDs.

Potential Impact of PT

In order to make an impact on incidence of TB, PT has to be administered to a large number of people. In a high-density population served by a single health centre in sub-Saharan Africa, for example, there may be 200,000 people and around 500 new cases of TB annually. In order to prevent 10-20% of these cases (a target that would allow one to notice the difference), the estimates above suggest that the PT service would need to screen 1500-3000 HIV positive people, which means that the VCT services would need to test about 4,000 - 8,000 people per year. This number might be distributed between those being tested in maternal health services, stand-alone VCT sites, general health clinics etc.

In the short term, delivery of PT will be limited by the number of sites where a sufficient number of people know their HIV status, or where there is sufficient demand for and capacity of VCT services. PT should therefore be promoted as an intervention for those living with HIV, rather than as a primary strategy to control the public health burden of tuberculosis.

Delivery of PT services

The priority for TB control programmes remains the detection and treatment of active cases, as formulated in the DOTS strategy. An efficient TB programme is an effective strategy to reduce transmission of TB. If the introduction of a PT service leads to less effective detection and treatment of active cases of TB, ongoing transmission will quickly outweigh any reduction in incidence of TB. PT services should be therefore be developed in such a way that synergy is created with the TB diagnosis and treatment services. In particular, PT services should not drain resources from over-stretched TB services. The capacity of the various organisations both governmental and non-governmental involved in care and prevention of TB and HIV/AIDS will vary from site to site. It is not therefore possible to provide a single model but some general criteria should apply:

- Initial screening of potential recipients of PT will be carried out by the voluntary counselling and testing services, which may be within government health services or not
- Patients who have been coughing for more than three weeks should have three sputum samples examined in a quality assured laboratory
- Chest radiographs should be performed in all potential recipients
- Patients who are found to have active TB during their screening for PT must have easy access to a treatment programme that has a high chance of curing them
- Individuals with symptoms compatible with TB should not receive PT, even if a diagnosis is not made
- Supplies of drugs for PT will usually be provided through the same mechanism that supplies the TB treatment service and must be ordered and accounted for in a similar manner
- Supervision of people taking PT may be carried out within the counselling and testing service, but must not detract from supervision of patients being treated for active TB

Drug regimens

Although eight different regimens have been proven to reduce the risk of active tuberculosis in tuberculin-positive, HIV-positive adults, isoniazid is the regimen recommended in developing countries. Isoniazid may be given as daily, self-administered therapy for six months at a dose of 5mg/kg to a maximum of 300mg. These individuals should be seen monthly and given one month supply of medication at each visit. Adherence may be improved by giving an additional two week emergency buffer supply to be used if the individual has to defer his or her monthly review.

Rifampicin containing regimens are not recommended in order to eliminate the risk of promoting rifampicin resistance, through inadequate screening procedures or by misuse of the tablets.

Preventive therapy is contraindicated in patients with active tuberculosis and in patients with active (chronic or acute) hepatitis. Active tuberculosis must be excluded before beginning preventive therapy. Isoniazid should be given with caution to individuals who consume alcohol daily.

Patients should be monitored at the routine visits for adherence with treatment, drug toxicity, and signs or symptoms of active tuberculosis. Patients who interrupt therapy may be restarted with the aim of providing at least six months of isoniazid therapy during a one year period. Pill counts and self-report may be useful in assessing adherence.

Clients with symptoms of tuberculosis or toxicity to medication should be evaluated immediately. Preventive therapy should not be continued if the patient develops signs or symptoms of tuberculosis. These suspected cases must be properly evaluated for active tuberculosis and referred to the National TB Program for registration and treatment.

Although biochemical monitoring of liver enzymes for hepatitis is not routinely recommended, patients should be carefully educated about the symptoms of hepatitis and instructed to discontinue the drug promptly should these occur.

In addition, there should be regular counselling and education about the symptoms of drug toxicity, in particular hepatitis, and active tuberculosis. Every opportunity to educate and counsel patients about HIV and its complications should be taken during preventive therapy.

Programs or centres that offer PT should assess the effectiveness of PT regularly. This assessment should include attendance at scheduled appointments, adherence (number of persons started on preventive therapy and number completed), toxicity and withdrawals from therapy due to toxicity and number of suspected TB cases in screening and monitoring of therapy. Individual records should be maintained to document use of PT. Individual information would be aggregated for regular reports, which may be used by the TB programme to estimate future drug requirements.

Conclusions

In 1993, WHO and the IUATLD issued a joint statement which supported the recommendation of isoniazid PT for persons with both HIV and tuberculosis infections. Since then several randomised controlled clinical trials have confirmed the efficacy of PT and a few studies have quantified the feasibility of implementing PT in a less controlled setting.

The evidence shows that PT is not an alternative to the DOTS strategy for controlling TB, even in areas with a high prevalence of HIV. However, many opportunities for providing PT to people living with HIV have been missed and this has led to many cases of TB that could have been prevented

The difference between the conclusions of the meeting in February 1998 and the 1993 guidelines is one of emphasis, rather than content. PT should be part of the package of care available to PLWH. The next steps should be to develop systems that greatly increase the accessibility of PT to people living with HIV in settings of high TB prevalence, while ensuring that the efficiency of TB control programmes is not compromised. To do so will require greater collaboration between those fighting TB and those fighting HIV/AIDS.

References

- Aisu T, Raviglione MC, Van Praag E, et al. Preventive chemotherapy for HIV-associated tuberculosis in Uganda: an operational assessment at a voluntary counselling and testing centre. *AIDS* 1995, 9:267-273.
- Aisu T, 1998. Ongoing studies presented at meeting.
- Anonymous. Tuberculosis preventive therapy in HIV-infected individuals. A joint statement of the WHO Tuberculosis Programme and the Global Programme on AIDS, and the International Union Against Tuberculosis and Lung Disease (IUATLD). *Weekly Epidemiological Record* 1993, 68:361-364.
- Antonucci G, Girardi E, Ippolito G, et al. Fattibilità della terapia preventiva della tubercolosi in soggetti con infezione da HIV: risultati preliminari di uno studio multicentrico. *Giornale Italiano di Malattie Infettive* 1997, Suppl 1, Vol 3:137-142.
- Antonucci G, Girardi E, Raviglione MC, Ippolito G. Risk factors for tuberculosis in HIV-infected persons: a prospective cohort study. *JAMA* 1995;274:143-148.
- Braun MM, Badi N, Ryder RW, et al. A retrospective cohort study of the risk of tuberculosis among women of childbearing age with HIV infection in Zaire. *Am Rev Respir Dis* 1991 Mar; 143(3):501-504.
- Bucher 1998. Ongoing studies presented at meeting.
- Chawalit N. 1998. Ongoing studies presented at meeting.
- De Cock K, Grant A, and Porter JDH. Preventive therapy for tuberculosis in HIV-infected persons: international recommendations, research, and practice. *The Lancet* April 1995; Vol. 345:833-836.
- Floyd K, Wilkinson D, and Gilks C. Comparison of cost-effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: experience from rural South Africa. *Brit Med Journ* 1997, Vol 315:1407-1411.
- Foster S, Godfrey-Faussett P, and Porter J. Modelling the economic benefits of tuberculosis preventive therapy for people with HIV: the example of Zambia. *AIDS* 1997, 11:919-925.
- Godfrey-Faussett P, Baggaley R, Mwinga A, et al. Recruitment to a trial of tuberculosis preventive therapy from a voluntary HIV testing centre in Lusaka: Relevance to implementation. *Trans R Soc Trop Med Hyg* 1995, 89:354-358.

Gordin FM, Mats JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. *New Eng Journ Med* 1997; No. 5, Vol. 337:315-320.

Gordin FM. 1998. Ongoing studies presented at meeting.

Guelar A, Gatell JM, Verdejo J, et al. A prospective study of the risk of tuberculosis among HIV-infected patients. *AIDS* 1993, 7:1345-1349.

Halsey NA, Coberly JS, Desormeaux J, et al. Intermittent preventive therapy for tuberculosis: A randomized trial of isoniazid vs rifampin and pyrazinamid in persons infected with human immunodeficiency virus. *Lancet* 1998; 351:786-92.

Hanvanich 1998. Ongoing studies presented at meeting.

Hawken MP, Meme HK, Elliott LC, et al. Isonizid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trials. *AIDS* 1997; 11:875-882.

Markowitz N, Hansen NI, Hopewell PC, et al. Incidence of tuberculosis in the United States among HIV-infected persons. *Ann Intern Med.* 1997; 126:123-132.

Moreno S, Miralles P, Diaz MD, et al. Isonizid preventive therapy in human immunodeficiency virus-infected persons. *Arch Intern Med/Vol 157, 11/25 1997.*

Moreno S, Baraia-Extaburu J, Bouza E, et al. Risk for developing tuberculosis among anergic patients infected with HIV. *Ann Intern Med* 1993;119:194-198.

Murray CJ, DeJonghe E, Chum HJ, et al. Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet* 1991 Nov 23; 338(8778):1305-1308.

Mwinga A, 1998. Ongoing studies presented at meeting.

Ngamvithayapong J, Uthairoravit W, Yanai H, et al. Adherence to tuberculosis preventive therapy among HIV-infected persons in Chiang Rai, Thailand. *AIDS* 1997, 11:107-112.

O'Brien RJ, Perriens JH. Preventive therapy for tuberculosis in HIV infection: the promise and the reality. *AIDS* 1995; 9:665-673.

Pape JW, Jean SS, Ho JL, et al. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progress of HIV infection. *Lancet* 1993;342:268-72.

Sawert H, Girardi E, Antonucci G, et al. Preventive therapy for tuberculosis in HIV-infected persons: an analysis of policy options based on tuberculin status and CD4+ cell count. *Arch Int Med* 1988 (in print)

Selwyn PA, Hartel D, Lewis VA, et al. A Prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *New Eng Journ Med* 1989; 320:545-550.

Selwyn PA, Sckell BM, Alcibes P, et al. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *JAMA* 1992;268:504-509.

Wadhawan D, Hira S, Mwansa N, Perine P. Preventive tuberculosis chemotherapy with isoniazid among persons infected with HIV-1. VIII International Conference on AIDS. June 1992, Amsterdam (abstract TuB 0536).

Wilkinson D. Preventive therapy for tuberculosis in HIV infected persons. In: Garner P, Gelband H, Alliaro P, Salinas R, Wilkinson D (eds). *Tropical Diseases Module of the Cochrane Database of Systematic Reviews*. Available in the Cochrane Library (database on disk and CD-ROM. The Cochrane Collaboration, Issue 4. Oxford: Update Software; 1997. Updated quarterly. Available from: BMJ Publishing group, London.

Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *New Eng Journ Med* 1997; No. 12, Vol. 337:801-808.

List of Participants

Dr Justine Agness-Soumahoro, Chef de Service du CSUS/USAC/HDY, BP V3, Abidjan, Cité de Tréchéville, Côte d'Ivoire.

Dr Thomas Aisu, National Tuberculosis and Leprosy Programme, Ministry of Health, P.O. Box 16069, Wandegaya, Kampala, Uganda.

Dr Pasakorn Akarasewi, Director, Tuberculosis 10 Chiangmai, 143 Sridonchai Road, Chiangmai, Thailand 50000.

Dr Mary Grace Alwano-Edyegu, AIDS Information Centre, P.O. Box 10446, Kampala, Uganda.

Dr Giorgio Antonucci, Centro Di Riferimento AIDS, Ospedale "Lazzaro Spallanzani", Via Portuense, 292-0149 Roma, Italy.

Dr Amy Bloom, Global programme for Health, USAID, Ronald Reagan Building, 1300 Pennsylvania Avenue, Washington, D.C. 20523, USA.

Dr Heiner Bucher, Medizinische Universitaets-Poliklinik, Kantonsspital Basel, CH-4031, Basel, Switzerland.

Dr Hisbello Da Silva Campos, Centro de Referencia Prof. Helio Fraga, Est. De Curicica, 2.000, 22710-550 Rio de Janeiro, Brazil.

Dr Richard E. Chaisson, Director, AIDS Service, Johns Hopkins University, 600 N. Wolfe Street, Carnegie 292, Baltimore, MD 21287-6220, USA.

Dr Gavin Churchyard, P.O. Box 87, Welkom, Freestate 9460, South Africa.

Dr David Cohn, Denver Disease Control Services, 605 Bannock Street, Denver, Colorado 80204, USA.

Dr D. Coulibaly, Comité National de Lutte contre le SIDA les MST et la Tuberculose, Ministère de la Santé Publique, 04 B.P. 2113, Abidjan 04, République de Côte d'Ivoire.

Dr Kevin De Cock, Centre for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA.

Dr Susan Foster, Dept. of Public Health and Policy, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom.

Dr Enrico Girardi, Centro Di Riferimento AIDS, Ospedale "Lazzaro Spallanzani", Via Portuense, 292-00149 Roma, Italy.

Dr Fred Gordin, Infectious Diseases (151B), 50 Irving Street NW, Washington D.C. 20422, USA.

Dr Mattana Hanvanich, Department of Medicine (Infectious Unit), Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Fr Michael Kelly, Kara Counselling and Training Trust, P.O. Box 37559, Lusaka, Zambia.

Dr Daniel Kibuga, Head, National Leprosy and Tuberculosis Programme, Ministry of Health, Afya House, Cathedral Road, LG 05, P.O. Box 20781, Nairobi, Kenya.

Professor Bernard Larouzé, Institut de Médecin et Epidémiologie Africain, Hospital Claude Bernard, Paris, France.

Dr Refiloe Matji, Director, TB Programme, Private Bag X828, Pretoria 0001, Republic of South Africa.

Dr Alberto Matteelli, Department of Infectious and Tropical Diseases, Faculty of Medicine, University of Brescia, 25125 Brescia, Italy.

Dr Francis Mubiru, The AIDS Support Organization, Mulago, P.O. Box 10443, Kampala, Uganda.

Dr Alwyn Mwinga, ZAMBART Project, Department of Medicine, University Teaching Hospital, P.O. Box 50110, Lusaka, Zambia.

Dr Chawalit Natpratan, Director, Office of Communicable Disease Control, Region 10, 447 Chiangmai-Lampoon Road, Muang District, Chiangmai, Thailand 50000.

Dr Peter Nsubuga, Epidemiologist, TB Projects, Uganda CWRU Research Collaboration, P.O. Box 663, Kampala, Uganda.

Dr Richard J. O'Brien, Division of TB Elimination (E-10), Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA.

Dr A. Okwera, Head, TB/Chest Unit, Mulago Hospital, Uganda-CWRU Research Collaboration, P.O. Box 663, Kampala, Uganda.

Dr John Porter, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT.

Dr Hans L. Rieder, IUATLD, 68 Boulevard St Michel, 75006 Paris, France.

Dr Badara Samb, Institut de Medicin et Epidemiologie Africain, Hospital Claude Bernard, Paris, France.

Ms Rose Smart, Director, HIV/AIDS and STD Programme, Private Bag X828, Pretoria 0001, Republic of South Africa.

Dr Chana Tanchanpong, Director General, Department of Communicable Disease Control, Ministry of Public Health, Nonthaburi 1100, Thailand.

Dr Elizabeth Tayler, Knowledge Branch, Health and Population Division, Department for International Development, 94 Victoria Street, London SW1E 5JL, United Kingdom.

Dr Heinz Vergin, Consultant Economist, 1112 Gatewood Drive, Alexandria, VA 22307, USA.

Dr Chris Whalen, TB Research Unit, Case Western Reserve University, School of Medicine, Division of Infectious Diseases, 10900 Euclid Avenue, Cleveland, Ohio 44106-4984, USA.

Dr Jintana Yanai Ngamvithayapong, Research Associate, The Research Institute of Tuberculosis, 1050 Ban Boon Thong, Satarn-Payaban Road, Muang District Chiang Rai, Thailand.

Mr Wingstone Zulu, Network of Zambian People Living with HIV/AIDS, P.O. Box 32717, Lusaka, Zambia.

Secretariat

Dr A. Kochi, Director, Global Tuberculosis Programme

Dr P. Godfrey-Faussett, Tuberculosis Research Unit, Global Tuberculosis Programme

Dr P. Nunn, Tuberculosis Research Unit, Global Tuberculosis Programme

Dr M. Raviglione, Surveillance Epidemiology & Respiratory Health Unit, Global Tuberculosis Programme

Dr S. Spinaci, National Programme Support, Global Tuberculosis Programme

Dr P. Piot, Executive Director, UNAIDS

Dr Jos Perriens, Policy Research and Strategy, UNAIDS

Dr Eric Van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases

Dr R. Baggaley, Office of HIV/AIDS and Sexually Transmitted Diseases

Dr E. Nyarko, Regional Tuberculosis Adviser, AFRO

Dr E. Maganu, WHO Adviser to SATCI, WHO Liaison Office

Dr J. Narain, Regional Adviser on HIV/AIDS, SEARO

Dr H. Sawert, Division of Tuberculosis, Department of Communicable Disease Control, Ministry of Public Health