

HIV-TB Co-INFECTION: MEETING THE CHALLENGE

REPORT OF
THE FORUM FOR COLLABORATIVE HIV RESEARCH AND
TB/HIV WORKING GROUP OF THE STOP TB PARTNERSHIP
SYMPOSIUM AND ROUNDTABLE DISCUSSIONS ON HIV/TB*

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*IN COLLABORATION WITH

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¹ A webcast of the symposium is available at http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=2224
Slides from the presentations may be accessed at www.hivforum.org

EXECUTIVE SUMMARY

The Forum for Collaborative HIV Research in collaboration with the TB/HIV Working Group of the Stop TB Partnership and other sponsors convened a symposium and roundtable discussion under the theme “**HIV-TB Coinfection: Meeting the Challenge**” at the 4th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention in Sydney, Australia in July 2007. This meeting followed discussions initiated two years earlier at the 3rd IAS Conference in Rio de Janeiro, with the common goal of advancing the research agenda for emerging issues in HIV-TB coinfection. This report summarizes the meeting presentations and discussions.

Meeting context and objectives

The disproportionately low level of resource allocation to TB-related research and programs is a major cause for concern, and in high HIV/TB prevalence settings the consequences of this are devastating. TB is the most common opportunistic infection worldwide among HIV-infected patients starting antiretroviral therapy. In children and adults, HIV-TB coinfection remains associated with unacceptably high mortality. Health care workers are overwhelmed and ill-equipped to deal with the diagnostic and treatment challenges posed by the concurrence of the two diseases, and worrisome patterns of TB drug resistance are emerging, most notably exemplified in the outbreak of extensively resistant (XDR) TB in Tugela Ferry, South Africa in 2006. The goal of the recent meetings was to bring together, with a sense of urgency, key representatives from the fields of HIV and TB to determine opportunities for research collaborations addressing the multiplicity of challenges presented by the HIV/TB epidemic.

Background

Ongoing HIV research has not prioritized TB research questions, although TB represents the most serious opportunistic infection in HIV-infected patients. In addition, major efforts have been underway and funds invested to scale up programs for HIV treatment and care in resource-limited settings, however, these too have missed important opportunities to specifically address HIV-TB. In high HIV prevalence settings, the HIV-TB epidemic has already destabilized previous successes achieved by existing TB control programs, and potentially threatens to offset the gains that are being made in the rollout of HIV care and treatment.

Meeting presentations² illustrated the scale of the HIV/TB problem, and the challenges encountered in high HIV/TB prevalence regions with the immense increase in TB caseload that has occurred over the course of the HIV epidemic. The lack of sensitive tools applicable at the point of care for the diagnosis of TB in HIV-infected adults and children is one of the most significant obstacles. The alarming outbreak of extensively drug resistant (XDR) TB in South Africa in 2006 uncovered significant gaps in TB control programs.

For the management of patients with HIV-TB coinfection, studies are ongoing to determine which antiretroviral treatment (ART) regimen is optimal in combination with rifampin-based TB regimens, whether ART should be started with TB treatment or deferred and the role of isoniazid preventive therapy (IPT) in adults and children with access to ART.

Few studies of childhood TB have ever been conducted, yet TB is a common cause of acute pneumonia in HIV-infected children, and childhood TB contributes significantly to TB caseload. Little is known of the virological and immunological outcomes of pediatric HIV-TB coinfection, or of the pharmacokinetics of TB and HIV drugs. Indeed, too few drugs have been manufactured in pediatric formulations. Bacille Calmette-Guérin (BCG) vaccination, administered to all neonates in Africa, has recently been associated for an increased risk of disseminated BCG associated with high mortality in HIV-infected vaccinees.

Overall, the research efforts currently underway in both adult and pediatric populations are completely insufficient in the face of the serious challenges posed by the HIV/TB epidemic.

Research Priorities

The HIV/TB research agenda spans basic science, drug discovery, epidemiology and diagnostics research through to clinical trials and operational research. Priority areas for research that were highlighted during the discussions are outlined below.

1. Diagnostics and laboratory capacity

² Slides from meeting presentations can be accessed at www.hivforum.org; a webcast of the symposium is available at http://www.kaisernet.org/health_cast/hcast_index.cfm?display=detail&hc=2224

Existing diagnostic tests for TB are antiquated, and the standard smear microscopy has low sensitivity in immunocompromised populations, where smear negative pulmonary TB and extrapulmonary disease are common. Culture methods for detection of *M. tuberculosis* and drug susceptibility are slow. In many high prevalence settings, there is a dire need to strengthen laboratory capacity as few laboratories are equipped to detect drug resistant TB.

Recommendations:

- Pending the availability and expansion of rapid, simple and accurate laboratory testing for MDR/XDR-TB, develop screening tools to identify potential cases of infectious or drug resistant TB based on clinical algorithms and microscopy.
- Equip laboratories to establish capacity to detect MDR/XDR-TB based on standardized testing methods, with consideration of the technical difficulties that this will involve.
- Develop safe rapid tests that use molecular methods to detect both first and second line drug resistance. These tests must be usable at the point of care.

2. *Epidemiology*

Population-based data on the incidence of TB, and in particular of resistant TB, is lacking particularly in high burden countries in Africa.

Recommendations:

- Rapidly map hotspots using procedures appropriate for outbreak investigations rather than slower methods for standard surveillance.
- Develop new approaches for intensified case-finding in high prevalence settings as an adjunctive strategy to DOTS.

3. *Infection control*

Infection control has been widely neglected as a priority, but interruption of transmission at healthcare facilities is paramount, particularly as it has been linked to recent outbreaks of HIV-associated resistant TB.

Recommendations:

- Address practical questions related to the implementation of infection control procedures: how to screen patients, how to protect healthcare workers and what is

the efficacy of environmental controls such as ventilation and UV germicidal irradiation.

- Develop strategies for monitoring site infection control once procedures have been established.

4. *Isoniazid preventive therapy (IPT)*

The implementation of IPT remains a controversial issue, although strong evidence supports the rationale for IPT in latent TB infection. Concerns over the applicability of IPT in high prevalence settings remain, where tools and resources are lacking to rule out active TB before initiating IPT, and there is fear of the development of drug resistance. However, IPT can significantly reduce the incidence of TB in HIV-infected individuals, and the existing DOTS strategy for TB control needs to be expanded as it is failing to curb TB incidence in settings with high HIV prevalence.

Recommendations:

- Urgently develop diagnostic tools to exclude active TB before initiation of IPT in HIV-infected patients.
- Study the risk of isoniazid resistance in regions with a high prevalence of HIV-associated TB in order to move this prevention strategy forward.
- Investigate the duration of treatment, monitoring of uptake and co-administration with cotrimoxazole and ARVs; some of these questions could be addressed in cohort studies.
- Develop effective protocols to roll out IPT.
- Resources, advocacy, and community mobilization to push for implementation and to prioritize additional research supporting IPT.

5. *TB in HIV-exposed and infected children*

Childhood TB remains a problem to diagnose and to treat, particularly in HIV-coinfected infants and children. Little is known of the long-term outcomes of TB and HIV treatment in children, and of the pharmacokinetics of TB drugs in this population. Preventive vaccination with the BCG vaccine is associated with serious risks in HIV-infected infants although it is routinely administered at birth in high HIV prevalence countries and indeed in most resource-limited settings.

Recommendations:

- Conduct prospective studies on the virological, immunological and microbiological outcomes of HIV-TB coinfection in children.
- Urgently develop diagnostic tests for TB in HIV-infected children.
- Determine the pharmacokinetics of both TB and HIV drugs in children.
- Evaluate the role of BCG vaccination, including whether administration can or should be delayed and the level of protection and benefit afforded by the vaccine.

6. Models for collaboration between TB and HIV programs

Both research and programs for the two diseases of HIV and TB have evolved separately, and funding patterns frequently reinforce the vertical approach to addressing these overlapping epidemics. As a result, the concept of “integration” of programs combating the two diseases is highly controversial. However, there is consensus that some degree of collaboration is necessary, and recognition that the way in which this is achieved will have to depend on the setting.

Recommendations:

- Effective evidence-based models are needed at local, district and national levels, in rural and urban settings, to demonstrate ways in which HIV and TB programs can positively interact and deliver services.

The role of HIV research networks to address urgent issues in HIV-TB coinfection

While potential opportunities abound within existing research programs to address the unanswered questions regarding HIV/TB, all of these programs lack either the funding or technical support needed to take advantage of these. This is true for HIV research networks for treatment and prevention and observational cohort studies. There are additional opportunities to conduct operational research at the country level that have also not been utilized. Only significant increases in allocation of funding for research and technical support for countries in designing operational research for programs being implemented will sufficiently address the urgent issues in HIV/TB.

Panel discussion of key agencies and sponsors in Sydney

Representatives from key sponsors and agencies outlined their commitments to HIV/TB and mechanisms for support. The agencies represented included:

- The Agence Nationale de Recherches sur le Sida et les Hépatites Virale (ANRS)
- The Bill and Melinda Gates Foundation (BMGF)
- The European and Developing Countries Clinical Trials Partnership (EDCTP)
- The Global Fund to Fight AIDS, Tuberculosis and Malaria
- The National Institutes of Health (NIH)
- The World Bank
- The World Health Organization (WHO)
- UNAIDS

These organizations pledged their commitment to HIV/TB research and capacity building, and encouraged the involvement of civic society and NGOs in shaping the HIV/TB agenda. In line with the Sydney Declaration calling for increased resource allocation in HIV programming towards research, opportunities for operational research were highlighted.

Recommended next steps

To maintain and act on the momentum from the discussions in these meetings, several suggestions for next steps are listed here:

- The Forum and The TB/HIV Working Group of the Stop TB Partnership seek funding to sponsor meetings at CROI, IAS and other conferences where networking can continue and follow-up of activities reviewed
- Meeting participants with expertise in laboratory procedures propose quality control guidelines for assessment of AFB smear and TB culture and susceptibilities for research studies
 - The development of an informal or formal network of reference TB laboratories for research, and funding needed to develop this would be included in discussions of this group
- The newly revised guidelines on TB infection Control (WHO/CDC) be reviewed and disseminated to research groups for utility at research sites
- Standard guidelines for TB screening (WHO) be developed and disseminated to research groups for screening research participants in HIV studies
- The group organizes a scientific meeting on HIV/TB in occur in conjunction with the next IAS pathogenesis conference in Cape Town, South Africa in 2009

INTRODUCTION

A series of meetings have recently been convened in recognition of the need to bring together experts in the fields of HIV and TB to push forward a common research agenda for emerging issues in HIV-TB coinfection. Despite WHO's outlining of priorities for a global HIV/TB research agenda in 2004 [1], there has been insufficient progress in putting this agenda into action. HIV researchers have failed to address TB as a problem requiring urgent attention, due either to limited awareness or competing priorities, with the traditional divide between the HIV and TB communities only reinforced by silo approaches to funding and programs.

At the 3rd IAS Conference on HIV Pathogenesis, Treatment and Prevention in Rio de Janeiro in 2005, the Forum for Collaborative HIV Research in collaboration with the Agence Nationale de Recherches sur le SIDA et les Hépatites Virale (ANRS) and the International AIDS Society (IAS) sponsored a symposium and research discussion roundtable on HIV-TB under the theme "Confronting the problem through an integrated research approach". This was the first time that major sponsors came together to analyze and discuss the scale of the problem specifically as it relates to the conduct of HIV/TB research.

At the recent 4th IAS Conference in Sydney in July 2007, the Forum for Collaborative HIV Research together with the TB/HIV Working Group of the Stop TB Partnership and several other partners³ organized a follow up meeting "**HIV-TB Infection: Meeting the Challenge**". This meeting included an initial open symposium for all IAS conference participants followed by a research discussion roundtable to focus on specific topics in HIV/TB research. The complete spectrum of research from basic science, drug discovery and new diagnostics through to clinical trials and operational research was considered during the meetings.

This report summarizes the presentations and discussions on "**HIV-TB Infection: Meeting the Challenge**" that took place on July 22-23, 2007 in Sydney. Urgent action on the part of funding agencies, researchers, policy makers and communities is needed to face the challenges posed by the dual epidemic of HIV-TB that are outlined here.

³ Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), Bill and Melinda Gates Foundation (BMGF), Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE), European and Developing Countries Clinical Trials Partnership Program (EDCTP), International AIDS Society (IAS), National Institutes of Health (NIH), Tibotec and the World Health Organization (WHO)

BACKGROUND

Why is an HIV/TB research agenda important?

The global impact of the converging dual epidemics of tuberculosis (TB) and human immunodeficiency virus (HIV) is one of the major public health challenges of our time. The World Health Organization (WHO) reports 8.8 million new cases of TB and 1.6 million TB-related deaths in 2005, of which 195,000 were HIV-infected patients. Tuberculosis is the most common opportunistic infection in patients starting antiretroviral treatment (ART) worldwide [2]. It is also a leading cause of death in HIV-infected patients. The HIV epidemic has completely destabilized TB control in high HIV prevalence regions. Today, 50% or more of new TB cases are also HIV coinfecting in southern and eastern Africa, which is the center of the HIV/TB epidemic. The DOTS strategy adopted by TB control programs in the majority of countries has not been sufficient to control HIV-associated TB particularly in countries in sub-Saharan Africa, as a result of the unprecedented increases in TB caseload. Although the global incidence of TB has taken a downward trend in recent years, incidence has increased in sub-Saharan Africa in areas of high HIV prevalence. As a result there are currently more new TB cases each year than ever before [3].

Reports of increasing rates of both multi-drug resistant TB (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are further cause for alarm demanding urgent action. While MDR-TB refers to resistance to at least the two first line agents isoniazid and rifampin, XDR-TB has been defined as TB strains lacking susceptibility to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin), in addition to MDR-TB. In 2006, WHO and the US Center for Disease Control (CDC) first reported global estimates for the number of cases of XDR-TB between 2000 and 2004. Of the 17,690 TB isolates tested in this survey, 20% were MDR and 2% XDR [4]. Data from Africa and Southeast Asia were not available for the representation of XDR-TB cases in this report. However, the alarming outbreak of XDR-TB in Tugela Ferry, South Africa in 2006 uncovered higher than expected rates of both MDR- and XDR-TB in South Africa, both associated with HIV infection. All diagnosed cases of XDR-TB occurred in HIV-infected individuals, with an extremely high mortality rate of 98% reported in the 53 cases identified, and a median survival time of only 16 days from time of diagnosis [5]. Since the initial report, there have now been over 450 cases of MDR-TB in Tugela Ferry, of which over 260 cases, or 55%, are XDR-TB. Thus in two years, figures for XDR-TB have increased five fold. Mortality for XDR-TB has been reduced slightly from 98% to approximately 85%,

however mortality among MDR-TB in this setting is also alarmingly high and approaches 65-70%, with 90% of cases HIV-coinfected [6].

In response to these sobering events, WHO convened a Global XDR-TB Task Force in 2006 and defined additional measures to scale up control of TB in order to prevent new cases of MDR-TB and XDR-TB and treat cases of MDR- and XDR-TB more rapidly.

Global estimates for resistant TB remain on the increase, as XDR-TB was confirmed in 41 countries as of October 2007, compared to 17 countries in March 2006. At least 400,000 individuals are estimated to be infected with MDR-TB and 26,000 infected with XDR-TB worldwide [7, 8]. However, the current real incidence and prevalence rates of MDR- and particularly XDR-TB are unknown due to the unavailability of population-based data, and many high burden TB regions in Africa and Southeast Asia are under represented in the data at hand. The extent of this under representation is illustrated by the fact that South Africa is the only country in the southern African region with the laboratory capacity to diagnose XDR-TB. Thus, the emergence of resistant TB has also uncovered significant gaps in TB control strategies that threaten the future success of both TB and HIV programs.

TB and HIV are both family diseases, and any case of HIV or TB detected is likely to uncover further cases within the same household. Prevalence and resistance patterns of TB in the adult community are reflected in children. TB is a common cause of acute pneumonia in both HIV-infected and -uninfected children, and in a South African study, 23.4/100 HIV-infected children developed TB every year [9, 10]. The convergence of HIV and TB results in additional problems in pediatric care, particularly in diagnosis. Since the majority of children with untreated HIV-infection suffer from chronic lung disease, the diagnosis of TB with the limited tools available in high-burden, resource-poor countries is a great challenge to providers. Data from South Africa confirm that childhood TB contributes significantly to caseload, with children comprising 14% of total TB disease burden in this setting [11]. In addition, drug resistant TB in children is increasing. Despite this, very few clinical trials of childhood TB have been conducted to optimize diagnosis or outcome of treatment.

A CASE STUDY FROM THE WESTERN CAPE, SOUTH AFRICA

To illustrate the immense challenges faced at various levels in resource-poor settings hardest hit by the convergence of the two epidemics, data was presented from a township in Cape Town, South Africa, with a population of approximately 13,000 people [12, 13].

At the level of the local TB clinic in this township, a six fold increase in the TB patient caseload was reported between 1996 and 2004, from 30 to 180 per year, with a disproportionate increase in sputum smear-negative TB (sputum smear examination is the method used to diagnose pulmonary TB) and extrapulmonary TB, which are difficult to diagnose. Furthermore, retreatment cases continued to increase from initial low rates of 3% up to 24%, of which 87% were among HIV-infected patients. Mortality rates in coinfecting patients are high, with up to 30% of such patients in sub-Saharan Africa being reported to die during the course of TB treatment in the pre-ART era [14].

At the community level in the same setting, TB incidence increased almost three-fold from 580/100,000 in 1996 to 1,468/100,000 in 2004. The rise in TB incidence mirrored that of HIV prevalence, which climbed from 6.3% to 21.9% in the same period. By age group, the sharpest increase in TB incidence was observed in adults between the ages of 20 and 49 years, but increasing numbers of cases were also recorded for adolescents – traditionally the age-group at lowest risk of TB. Notably, the number of TB notifications continued to rise even after HIV prevalence rates reached a plateau around 2001, probably reflecting increasing numbers of people with progressive immunodeficiency in the population, leading to both increased susceptibility to new infections and reactivation of latent infections.

In a recently published cross-sectional survey of the same community, HIV and TB prevalence were reported at 23% and 3%, respectively, based on a 10% population sample [13]. While the case finding proportion for TB in HIV-uninfected individuals reached 67%, this proportion was only 37% in those who were HIV-infected. Thus, there is a large burden of undiagnosed TB in the HIV-infected population.

DOTS as a TB control strategy has proven insufficient in this setting. In high prevalence regions such as this one, the scope of DOTS needs to be redefined and broadened to include additional approaches such as active case finding, where the population is actively screened for TB rather than relying on passive reporting of TB cases alone. The role of isoniazid preventive therapy (IPT), and the sources and sites for TB transmission also need to be mapped out.

Additional problems in managing HIV-TB coinfecting patients are encountered in HIV treatment programs. In this setting in South Africa, half of all patients starting antiretroviral drugs (ARVs) in the local HIV clinic had received at least one course of TB treatment, while a quarter presented with active TB. One in ten patients developed TB during the first year on treatment, with many of these cases presumably having presented for initial antiretroviral therapy (ART) screening with subclinical TB and remaining undiagnosed [15].

Even in patients that had received three years of ART, TB incidence remained higher than in the community or in HIV-uninfected individuals. The fact that this expanding cohort of patients with greatly increased life expectancy retains a chronically heightened risk of TB threatens to offset any potential benefits for TB control that might have been achieved through the rollout of ART.

What studies of HIV-TB coinfection are currently underway?

Treatment of HIV-TB coinfection is complex and associated with high pill burden, overlapping drug toxicities, risk of immune reconstitution inflammatory syndrome (IRIS, in which initiation of ART leads to a paradoxical deterioration of pre-existing infections such as TB, and may be life-threatening) and challenges related to adherence. To inform the treatment of adult patients, major questions to address include which antiretroviral drugs to administer, when to begin and how to manage IRIS, as well as to determine the duration and intermittency of TB treatment. The efficacy of once-daily ART, choice of non-nucleoside reverse transcriptase inhibitor (NNRTI) and dose, and pharmacokinetics of TB and HIV drugs need to be investigated. The summary table below shows an overview of currently ongoing studies of treatment in HIV-TB coinfecting patients, and the year of their expected results.

The CREATE Consortium is conducting several studies in adults to investigate strategies for control of HIV-related TB beyond DOTS. Main elements include intensified case finding, treatment of latent infection, household interventions for HIV/TB linked to cases and combined HIV and IPT treatment programs. Three large trials are underway to investigate mass preventive therapy (THIBELA, study of gold miners in South Africa), household interventions with intensified case finding (ZAMSTAR, in Zambia and South Africa), and preventive therapy in patients with access to antiretroviral therapy (THRio, Brazil). In addition, the National Institutes of Health (NIH) is sponsoring a large randomized controlled pediatric trial (IMPAACT 1041) seeking to enroll 1,300 infants in South Africa to determine the efficacy of INH in preventing TB disease and latent infection in children perinatally exposed to HIV-infection.

Meeting discussions highlighted major obstacles that have interfered with the timely approval and conduct of important interventional clinical trials around the world. The most important noted was access to drugs, both from the pharmaceutical industry and in-country treatment programs, which frequently do not provide drugs for subjects enrolled in clinical trials⁴. This was mainly attributed to incomplete local stakeholders involvement in the planning and proposal development. Additional logistical obstacles, processes for drug approval by various government regulatory agencies, the need to establish capacity for laboratory diagnostic testing, and training and education of staff

⁴ For more information on this topic, see <http://www.hivforum.org/projects/Accessing%20Drugs%20RLS.htm>

all contributed to delays in getting studies off the ground. Researchers also stressed the importance of ensuring sustainable resources for research efforts.

Clinical trials of a number of new TB drugs and treatment approaches are also underway [16, 17]. The newer fluoroquinolones gatifloxacin and moxifloxacin are being studied in Phase 2 and 3 trials with the goal of shortening treatment duration of pulmonary TB. After a forty-year lull in the development of new TB drugs, several sponsors are now supporting the research and development of novel compounds. Phase 2 studies are underway with TMC207 (Johnson & Johnson/Tibotec); other compounds in earlier development include OPC67683 (Otsuka Pharmaceuticals), PA824 (TB Alliance), LL3858 (Lupin) and SQ109 (Sequella).

While these ongoing efforts should be recognized, the current portfolio of HIV-TB research is utterly insufficient in view of the enormity of the problem being faced and the multiplicity of unanswered questions spanning the diagnosis, treatment and epidemiology of HIV-TB.

Summary table of ongoing clinical trials for treatment of patients with HIV-TB coinfection (adapted from Blanc [18])

Trial [Trial registration]	Sponsor	Country, Sample size	TB regimen	ART regimen	Arms	Duration	Primary outcome(s)	End date
¹ ANRS 1295 – CAMELIA [NCT00226434]	ANRS & NIAID/CIPRA	Cambodia (N=660)	Standard 2EHRZ/4HR	d4T/3TC + EFV	1. Early: HAART 2 weeks after initiating TB treatment 2. Late: HAART 8 weeks after initiating TB treatment	12	Survival	2009
² AACTG A5221 [NCT00108862]	NIAID	Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, Zimbabwe, US (N=800)	Rifampin or rifabutin-based regimen	TDF/FTC + EFV	1. Early: HAART within 2 weeks of initiating TB treatment 2. Late: HAART 8-12 weeks after initiating TB treatment	12	Survival without AIDS progression	?
³ START [NCT00091936]	NIAID	South Africa (N=592)	Standard 2EHRZ/4HR	ddI/3TC + EFV	1. Integrated: HAART concurrent with standard TB treatment, through DOT 2. Sequential: after completion of TB treatment, HAART without DOT	18	Diagnosis of an AIDS-defining illness, mortality at 18 months	?
⁴ TB-HAART [ISRCTN77861053]	WHO/TDR	South Africa, Tanzania, Uganda, Zambia (N=1900)	Standard 2EHRZ/4HR	ZDV/3TC + EFV or placebo	1. HAART initiated 2 weeks after initiation of TB treatment, concomitant with TB treatment until 6 months, then continuation with ART alone 2. HAART placebo initiated 2 weeks after initiation of TB treatment, concomitant with TB treatment until 6 months, then HAART	24	Composite endpoint of TB treatment failure or death at 6 months after initiation of TB treatment	2011
⁵ PART [NCT00078247]	NIAID & Makerere University	Uganda	Standard 2EHRZ/4HR	ZDV/3TC / ABV	1. Initial HAART 2. Delay HAART until CD4 count decreases to <200/mm ³	24	CD4 cell count decline (slope); time to AIDS	?
⁶ BKVIR [NCT 00115609]	ANRS	France (N=100)	Standard 2EHRZ/4HR	TDF/FTC + EFV	N/A	12	Treatment success rate; plasma HIV-1 RNA level <50 copies/ml; TB cured	2008
⁷ HIV-NAT 033 [NCT 00476853]	The HIV Netherlands Australia Thailand	Thailand (N=100)	Rifampin-based regimen	Nevirapine e-	1. Nevirapine dose 400 mg/day 2. Nevirapine dose 600 mg/day	12	Efficacy based on plasma HIV-1 RNA	2008

Abbreviations: 2EHRZ/4HR – 2 months of ethambutol, isoniazid, rifampin, pyrazinamide, then 4 months of isoniazid and rifampin. ART= antiretroviral therapy; d4T=stavudine; 3TC=lamivudine; EFV=efavirenz; TDF=tenofovir; FTC=emtricitabine; ddI=didanosine; ZDV= zidovudine; RTV=ritonavir; IDV=indinavir; ANRS –Agence nationale de recherches sur le sida et les hépatites virales B et C (France); NIAID/CIPRA – National Institute of Allergy and Infectious Diseases/Comprehensive International Program of Research on AIDS (US)

¹ “Early vs Late Introduction of Antiretroviral Therapy in Naive HIV-Infected Patients With Tuberculosis in Cambodia”

² “A Strategy Study of Immediate Versus Deferred Initiation of ART for HIV Infected Persons Treated for Tuberculosis With CD4 Less Than 200 Cells/mm³”

³ “Implementing Anti-Retroviral Therapy in Resource-Constrained Settings: A Randomized Controlled Trial to Assess the Effect of Integrated Tuberculosis and HIV Care on the Incidence of AIDS-Defining Conditions or Mortality in Subjects Co-Infected With Tuberculosis and HIV”

⁴ “An evaluation of the impact of early initiation of Highly Active Anti-Retroviral Therapy (HAART) on Tuberculosis (TB) treatment outcomes for TB patients co-infected with Human Immunodeficiency Virus (HIV)”

⁵ “Delaying HIV Disease Progression With Punctuated Antiretroviral Therapy in HIV-Associated Tuberculosis”

⁶ “Pilot Trial Evaluating Once Daily Triple Combination Antiretroviral Therapy With Tenofovir-Emtricitabine and Efavirenz in HIV-1 Infected Patients With Mycobacterium Tuberculosis Infection ANRS129 BKVIR”

Trial [Trial registration]	Sponsor	Country, Sample size	TB regimen	ART regimen	Arms	Duration	Primary outcome(s)	End date
	Research Collaboration			containing HAART regimen			level	
⁸ N2R [NCT00483054]	Bamrasnaradura Infectious Diseases Institute	Thailand	Rifampin-based regimen	NNRTI-based HAART	1. EFV-based HAART 2. NVP-based HAART	36 (primary endpoint 12)	HAART efficacy based on plasma HIV-1RNA < 50 copies/mL	?
⁹ trc23 [NCT00332306]	Tuberculosis Research Centre, India National AIDS Control Organisation, India Indian Council of Medical Research	India (N=180)	Standard 2EHRZ3/4RH3	NNRTI-based HAART, once-daily	1. EFV-based HAART, once-daily 2. NVP-based HAART, once-daily	12	HAART efficacy based on plasma HIV-1 RNA <400 copies/ml	2009
¹⁰ ANRS 12146 [NCT00495326]	ANRS & Medecins Sans Frontieres	Mozambique (N=570)	Rifampin-based regimen	NNRTI-based HAART	1. EFV-based HAART 2. NVP-based HAART	12	HAART efficacy based on plasma viral load	2009
¹¹ PETE [NCT00474435]	African Poverty Related Infection Oriented Research Initiative, Radboud University, Kilimanjaro Christian Medical Centre	Tanzania (N=30)	Rifampin-based regimen	TDF/FTC + EFV	N/A	6	PK parameters of antiretroviral and tuberculostatic agents	2008
¹² HIV-NAT 044 [NCT00411996]	The HIV Netherlands Australia Thailand Research Collaboration	Thailand (N=20)	Rifampin-based regimen	HAART containing RTV-boosted IDV	N/A	12	PK of indinavir-boosted indinavir	2007
¹³ OXTREC 023-04 (TB meningitis) [ISRCTN63659091]	University of Oxford & Wellcome Trust	Vietnam (N=247)	3EHRZ/6HR for TB meningitis	AZT/3TC +EFV	1. Immediate HAART 2. Deferred HAART (2 months)	9	Mortality (at end of TB treatment)	?

⁷ “A 48 Week, Randomized, Open-Label, 2 Arm Study to Compare the Efficacy, Safety and Tolerability of HAART Containing Nevirapine 400mg/Day Versus Nevirapine 600 mg/Day in HIV-1 Infected Patients Started at 2-6 Weeks After Initiating Rifampin Containing Antituberculous Therapy”

⁸ “Efavirenz-Based Versus Nevirapine-Based ART Among HIV-Infected Patients Receiving Rifampin (N2R)”

⁹ “Evaluation of Safety and Efficacy of Two Different Once Daily Anti Retroviral Treatment Regimens Along With Anti-Tuberculosis Treatment in Patients With HIV-1 and TB”

¹⁰ “Randomized Non-Inferiority Trial Comparing the Nevirapine-Based ART Versus the Standard Efavirenz-Based ART for the Treatment of HIV-TB co-Infected Patients on Rifampicin-Based Therapy (ANRS 12146)”

¹¹ “The Pharmacokinetics of co-Formulated Emtricitabine/Tenofovir + Efavirenz in HIV-Infected Patients With Smear-Positive Pulmonary Tuberculosis in Moshi, Tanzania”

¹² “The Pharmacokinetics and Safety of Ritonavir-Boosted Indinavir 600/100mg Bid Combined With NRTIs in ARV naïve HIV/TB co-Infected Patients Receiving Rifampicin Containing Anti-Tuberculosis Therapy”

¹³ “Study of immediate versus deferred antiretroviral therapy in HIV-associated tuberculous meningitis”

CURRENT QUESTIONS FOR HIV/TB RESEARCH

The research agenda for HIV/TB is broad, with questions ranging from the basic epidemiology of HIV-TB coinfection and the role of new and existing diagnostic tools and interventions through to health systems level research. A distinction can be made between both short, urgently needed, and long-term priorities for investigation. Several major areas for research are outlined below, reflecting presentations and discussion during the symposium and roundtable events in Sydney and Rio de Janeiro. Further analyses of current research questions in HIV/TB coinfection with contributions from many meeting participants can be found in a recent supplement to the *Journal of Infectious Diseases*: "Tuberculosis and HIV Coinfection" (*Journal of Infectious Diseases* 2007: Volume 196, Supplement 1).

DIAGNOSTICS AND LABORATORY CAPACITY

Standard TB diagnostic methods have developed little in the last 100 years. Yet, smear microscopy as the traditional cornerstone of TB diagnostic testing has more limited utility in immunocompromised populations, where the proportion of smear-negative pulmonary TB ranges from 24% to as high as 61% [19]. Sensitivity of this diagnostic test may be as low as 20%, and is compounded by additional challenges existing in the provision of quality microscopy. Culture methods for detection of *M. tuberculosis* and drug susceptibility testing (DST) are similarly antiquated, and slow to yield results. In many African countries, while it might be possible to diagnose HIV within an hour using a rapid test, it typically takes 3 weeks to obtain a diagnosis from a sputum smear or sputum culture. During that time, people with active TB, including MDR- and XDR-TB, may unknowingly continue to spread their infection.

WHO has developed standardized methods for DST, which should be part of routine program activities as recommended by the New Stop TB Strategy [20]. However, in the majority of resource-poor settings, there are huge deficits in laboratory capacity for DST, with grave implications for the detection of MDR/XDR-TB, typically limited to one or two national level laboratories in high burden countries in Africa. This was highlighted in the recent emergence of MDR and XDR-TB in South Africa.

There has been a complete lack of funding for quality assured TB laboratories, even in the research setting where large trials have been funded with endpoints directly linked to laboratory outcomes. Recent recommendations for TB DST to be conducted in laboratories with Biosafety Level 3 capability have huge cost implications. In addition, second-line DST has not yet been standardized internationally, although WHO is in the

process of developing guidance for DST for second-line drugs. It was suggested that enhanced respect for diagnostic research within the scientific community could serve to further stimulate progress in this field.

What is needed?

- Pending the availability and expansion of rapid, simple and accurate laboratory testing for MDR/XDR-TB, develop screening tools to identify potential cases of infectious or drug resistant TB based on clinical algorithms and microscopy.
- Equip laboratories to establish capacity to detect MDR/XDR-TB based on standardized testing methods, with consideration of the technical difficulties that this will involve.
- Develop safe rapid tests that use molecular methods to detect both first and second line drug resistance. These tests must be usable at the point of care.

EPIDEMIOLOGY

Recent experiences with XDR-TB outbreaks have uncovered significant gaps in TB control programs, and underscored the importance of TB epidemiologic characterization. There is a lack of population-based data reflecting the incidence of resistant TB particularly in high burden countries in Africa. Rapid investigation of hotspots should serve to better characterize transmission, i.e. nosocomial vs. community, and primary vs. acquired infection.

The role of active case-finding to increase case detection rates should also be considered, with approaches and screening tools that efficiently target HIV-infected patients and other groups with high TB prevalence. Case finding among household members provides an opportunity for improving case detection.

What is needed?

- Rapidly map hotspots using procedures appropriate for outbreak investigations rather than slower methods for standard surveillance.
- Develop new approaches for intensified case-finding in high prevalence settings as an adjunctive strategy to DOTS.

INFECTION CONTROL

Interruption of TB transmission is vital in ART programs where up to one third of patients have overlapping TB treatment with ART during the first year of treatment, creating an enormous hazard in clinics and hospital wards for patients and health care workers alike [15]. Yet, limited infection control is in place at most clinical sites. In fact, infection control has not been a focus of research or funding, although it represents the fastest, most efficient and least expensive measure that can be rapidly implemented to reduce nosocomial transmission, which has been heavily implicated in HIV-associated resistant TB. In the recent outbreak in South Africa, nosocomial transmission was a probable cause for transmission of XDR-TB, with two thirds of patients recently hospitalized before the onset of XDR-TB [5]. From a human rights perspective, it is unacceptable that patients or participants in research should be at risk of acquiring infection as a result of visiting a healthcare facility.

What is needed?

- Address practical questions related to the implementation of infection control procedures: how to screen patients, how to protect healthcare workers and what is the efficacy of environmental controls such as ventilation and UV germicidal irradiation.
- Develop strategies for monitoring site infection control once procedures have been established.

ISONIAZID PREVENTIVE THERAPY (IPT)

Despite strong evidence supporting the rationale for IPT in latent TB infection, implementation of IPT has not been widespread in countries with high TB burden, and opinions on IPT remain divided. This is due to recurring concerns over drug resistance, short duration of IPT efficacy, and difficulties in ruling out active TB in populations with high HIV prevalence with the limited diagnostic tools available. The problem is compounded by the lack of evidence to confirm that IPT does not increase resistance in high burden countries. Botswana remains the only one of the countries with the highest burden of HIV-associated TB to have adopted IPT at the national level.

A priority in this area is to address the exclusion of active TB before initiation of IPT in order to avoid suboptimal treatment of active TB that could lead to drug resistance. Once again, there is a need for sensitive diagnostic tools. For example, conflicting data has emerged on the need for screening chest radiography in addition to evaluation of

signs and symptoms for detection of active TB, significant in view of recently published high rates of subclinical TB in several regions.

New results from the THRio Study conducted in HIV-TB coinfecting in Brazil confirm the beneficial effect of combined IPT and ART [21]. More positive data has also emerged in the pediatric field pointing to the benefit of IPT as a routine strategy in HIV-infected children in South Africa [10], and another study is underway (IMPAACT 1041) examining the use of IPT as a primary strategy in both HIV-exposed and –infected infants.

A major barrier to implementation of IPT is linked to the availability of resources. Depending on the setting, TB and/or HIV programs need to be equipped to rule out active TB in HIV-infected patients, with adequately trained staff to administer treatment. This undertaking is arguably not as complex as the administration of ARVs, and highlights the need for advocacy and community mobilization in this area.

What is needed?

- Urgently develop diagnostic tools to exclude active TB before initiation of IPT in HIV-infected patients.
- Study the risk of isoniazid resistance in regions with a high prevalence of HIV-associated TB in order to move this prevention strategy forward.
- Investigate the duration of treatment, monitoring of uptake and co-administration with cotrimoxazole and ARVs; some of these questions could be addressed in cohort studies.
- Develop effective protocols to roll out IPT.
- Resources, advocacy, and community mobilization to push for implementation and to prioritize additional research supporting IPT.

TB IN HIV-EXPOSED AND INFECTED CHILDREN

TB exacerbates HIV-related mortality in HIV-infected children. HIV-infected children not on ART show poor responses to TB therapy, high mortality and high recurrence of TB [10]. While the diagnosis of TB in HIV-uninfected children has become easier with new approaches, such as the use of symptom complexes with high predictive value, problems remain for TB diagnosis in immunocompromised children. Many unanswered questions and problems also remain in treatment of pediatric HIV-TB coinfection; six months of treatment seem insufficient and increasing TB drug

resistance in children reflects overall increasing prevalence of drug resistant TB strains. The lack of pediatric drug formulations for both TB and HIV drugs remains a problem for providers.

Furthermore, little is known about the pharmacokinetics of TB drugs in children with HIV infection and/or with poor nutritional status; one study conducted in Malawi found lower blood levels of individual TB drugs in younger, HIV-infected children [22]. As in adults, drug interactions between antitubercular and antiretroviral drugs complicate concurrent treatment of the two diseases in children. Pediatricians repeatedly emphasize the importance of including children in studies of new drugs and of drug resistance early on and in parallel to studies in adults.

Another important issue unique to the setting of pediatric HIV-infection is the Bacille Calmette-Guérin (BCG) vaccine for TB disease, which is a component of the childhood vaccination regimen in most African countries and typically administered at birth. The safety of the vaccine in immunocompromised children has been called into question following disproportionately high rates of disseminated BCG associated with high mortality. This led WHO to issue an advisory note warning against its use in children known to be HIV-infected, although these may be difficult to identify at birth in such settings.

Overall, much new information is needed to inform prevention, diagnosis and treatment of pediatric TB. Many of the problems particular to research in children have been encountered in prevention of mother to child transmission (PMTCT) programs, and revolve around the need to improve fundamental health services for children dying of malnutrition, diarrhea and pneumonia in resource-poor countries. Thus quality of postnatal care for women and children is also key to defining both the epidemiology of TB and success rates of new interventions.

What is needed?

- Conduct prospective studies on the virological, immunological and microbiological outcomes of HIV-TB coinfection in children.
- Urgently develop diagnostic tests for TB in HIV-infected children.
- Determine the pharmacokinetics of both TB and HIV drugs in children.
- Evaluate the role of BCG vaccination, including whether administration can or should be delayed and the level of protection and benefit afforded by the vaccine.

MODELS FOR COLLABORATION BETWEEN TB AND HIV PROGRAMS

HIV and TB disease occur in a single patient, yet this contrasts the prevalent vertical approaches to programming and training of staff. WHO issued an interim policy for HIV/TB collaborative activities in 2004 [23]. The interim policy included recommendations for establishing mechanisms for collaboration, from the bidirectional perspectives of decreasing burden of TB in HIV patients and decreasing the burden of HIV in TB patients. The nationwide scale up of HIV-TB activities is now being promoted and has been initiated in many countries.

The concept of "integration" of services for HIV and TB proved controversial in the meeting discussions, the key question being what degree of integration could be beneficial without harming or overwhelming either of the individual traditionally distinct programs, and the subsequent impact on resource distribution and funding for each. Furthermore, differences in HIV prevalence between settings have practical implications for the kind of collaboration and organization required between HIV and TB programs, as do varying levels of expertise that may exist in each of the programs in different places. In addition, infection control remains a serious concern wherever programs are co-located. Overall, it was recognized that one model is unlikely to fit all settings. Suggestions were made to promote collaboration of programs by identifying tasks for each to address in order to promote cross-fertilization and rationalization of resources, rather than forcing both to coalesce into a single program. The inadvertent creation of a third program for HIV-TB should be avoided by clear definition of additional responsibilities faced by each of the two programs.

Several approaches in Africa with varying degrees of collaboration/integration between HIV and TB programs were briefly described in the discussion:

- Malawi at the national level has implemented separate TB and HIV programs both sharing public health approaches, with the HIV program is closely modeled on the previously existing TB program, with TB program strategies applied to the HIV program, including the reporting system.
- In an urban setting in Khayelitsha, South Africa, there is physical integration of HIV and TB care, with patients treated at the same location by the same staff.
- In rural KwaZulu-Natal, South Africa, there is partial integration of programs with attempts to bring the HIV and TB programs closer together.
- In Zimbabwe, TB clinics are used as an entry point to access HIV care and antiretroviral treatment, with patients referred to HIV programs upon completion of TB treatment.

The International Center for AIDS Care and Treatment Programs (ICAP) at the Columbia University Mailman School of Public Health has conceptualized HIV and

TB as diseases affecting families in the programs it supports in West, East and southern Africa. Family-centered, co-located care is provided for both adults and children, with an emphasis on retention of patients in treatment, engagement and support. Multi-disciplinary teams provide integrated HIV/TB care and treatment. A high proportion (approximately 60%) of patients enrolled are women. These programs highlight several opportunities for research, for example to determine incidence and prevalence of TB in the household after the introduction of HIV care, achieving earlier TB diagnosis in HIV-infected patients or evaluating prevention and adherence interventions.

A recurring theme during the discussions was the urgent need for additional resources to strengthen TB control efforts if current TB case detection rates of approximately 50% are to be maintained and improved upon, and for the conduct of operational research to assess implementation of approaches to care of HIV-TB coinfecting patients. It is paramount that programs funded by the Global Fund and PEPFAR include operational research components. Finally, the conduct of research alone to assess different approaches to care of HIV-TB coinfecting patients is not sufficient to guarantee successful implementation of programs. It was stressed that research studies should be planned strategically in consideration of information needed to drive advocacy and the political process to facilitate the translation of results into practice.

What is needed?

- Effective evidence-based models are needed at local, district and national levels, in rural and urban settings, to demonstrate ways in which HIV and TB programs can positively interact and deliver services.

THE WAY FORWARD

WHAT ARE THE PERSPECTIVES AND COMMITMENTS OF AGENCIES AND SPONSORS TO SUPPORT HIV/TB RESEARCH?

During a panel discussion at the Sydney satellite symposium "*HIV/TB Co-Infection: Meeting the Challenge*", representatives from key agencies and sponsors gave their perspectives of priorities and mechanisms for support and funding of HIV/TB research. TB research has been severely under funded, and research and development for all the three major diseases HIV, TB and malaria lags far behind the global programs in place to implement treatment [24]. In HIV research, higher relative levels of funding were achieved only through political advocacy and congressional pressure, highlighting the need to take an approach to generating data on HIV/TB that is different to relying solely on traditional investigator-initiated research, and that reflects consensus between donors and high burden countries on the priorities for research spending.

Summaries of statements from the various organizations follow. Common themes among the agencies present included commitment to research and capacity building, and encouragement for the involvement of civic society and NGOs in shaping the HIV/TB agenda.

Agence Nationale de Recherches sur le Sida et les Hépatites Virale (ANRS)

The French *Agence Nationale de Recherches sur le Sida et les Hépatites Virale (ANRS)* has a broad HIV research agenda and conducts studies at eight sites worldwide in Africa, South-East Asia and Brazil. The agency funds research proposals in which French researchers work with partners in low-income countries. Several trials are underway in HIV-TB coinfecting patient, including efficacy studies of ART regimens in when co-administered with rifampin-based TB therapy and studies investigating the optimal timing of ART initiation in HIV-infected patients starting TB treatment. Other topics currently investigated by ANRS-funded clinical trials include early ART initiation and/or 6-month isoniazid chemoprophylaxis in HIV-infected adults at early stages of immunosuppression (Temprano, ANRS 12136 in Ivory Coast) and one phase II study about the pharmacokinetics of rifabutin associated with TB drugs (ANRS 12150 in South Africa).

Bill and Melinda Gates Foundation (BMGF)

The *Bill and Melinda Gates Foundation* has shown strong support for HIV-TB coinfection through its funding of the Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE). BMGF is also dedicated to the development of improved diagnostic tests, more potent treatments that can shorten the duration of TB

treatment and show efficacy against resistant TB strains, and TB vaccines, and encourages the engagement of civil society in HIV/TB activities.

European and Developing Countries Clinical Trials Partnership (EDCTP)

The *European and Developing Countries Clinical Trials Partnership (EDCTP)* engages in capacity building and networking through its sponsorship of clinical trials. It employs a bottom-up approach in partner countries, establishing its activities based on initial stakeholder meetings. It has issued calls for proposal for the investigation of TB vaccines and TB treatment. EDCTP intends to establish centers of excellence for the conduct of clinical trials in West, East, Central and southern Africa, while improving the regulatory framework on the continent together with other partners.

The Global Fund to Fight AIDS, Tuberculosis and Malaria

The *Global Fund to Fight AIDS, Tuberculosis and Malaria* provides approximately two thirds of overall international funding for TB in 102 of its 130 eligible countries, with \$1.9 billion committed over five years. China represents a significant portion of this funding, with other large programs supported in India and Indonesia. While the Global Fund does not fund basic or clinical research, it can support operational research on programs being implemented that can be submitted as part of country requests within its system of rounds of funding. It was suggested that agencies such as WHO, UNAIDS, the World Bank and private foundations provide technical support to countries to assist in the development of HIV/TB programs for implementation, and that civil society is empowered to play a strong role in the design of these programs. The Global Fund mechanisms are not adapted for urgent responses to outbreaks and other emergencies, however discussions are underway with UNITAID to develop a mechanism for rapid drug distribution for resistant TB that can be linked to the Global Fund's round system.

National Institutes of Health (NIH)

The US *National Institutes of Health (NIH)* support a broad research portfolio on TB, with several randomized clinical trials underway addressing HIV-TB coinfection. Various institutes including the National Institute of Child Health and Human Development (NICHD), the National Heart, Lung and Blood Institute (NIHLB) and the Fogarty International Center are working with the National Institute for Allergy and Infectious Diseases (NIAID) to improve funding levels for HIV/TB. NIAID had recently developed a comprehensive research agenda around XDR-TB to identify gaps and to support research in areas such as TB diagnostics, treatments, prevention strategies and vaccines, in addition to investigation of basic biology and immunology of TB in HIV infection, the impact of the MDR epidemic on HIV and the clinical management of drug resistance.

The World Bank

The *World Bank* currently supports HIV/TB programs in a number of ways, through its sector-wide approach to strengthening the health sector and HIV/AIDS service delivery, and in its multi-country HIV/AIDS programs in Africa and the Caribbean, which include TB treatment. HIV Treatment Acceleration Programs incorporating TB services are underway in three African countries. It was acknowledged that HIV/TB has only recently become a subject of focus for the World Bank. As part of the World Bank's renewed strategic engagement on TB and HIV/TB, an Africa Regional TB team has been established and a TB public health specialist has been recruited. The World Bank will be expanding its involvement in three major areas: (i) strengthening analytic work to guide priority setting by focusing on economic and financial issues; (ii) leveraging resources and reducing funding gaps in the high TB burden/incidence countries; and (iii) supporting country assessments and impact evaluations of HIV/TB control interventions to enhance global knowledge. Additionally, the World Bank will increase efforts to integrate TB into country-led development agendas (e.g. Sector Wide Approaches Poverty Reduction Strategies, and Medium Term Expenditure Frameworks) by supporting countries through analytical work and policy dialogue. It will also continue to work intensively with the Stop TB Partnership, WHO, and GFATM to coordinate efforts to fight TB particularly in African countries struggling to contain the twin-epidemics of TB and HIV. At a global policy level, the World Bank is a member of the Stop TB Coordinating Board and is represented by the Sector Director for Human Development.

World Health Organization (WHO)

Three departments at *WHO* work on TB – the HIV/AIDS Department, the Stop TB Department and the Special Programme for Research and Training in Tropical Diseases (TDR). Among the public health issues raised as research priorities for HIV-TB coinfection was the question to what extent the approach to both diseases should be coordinated or integrated, ideally achieving integrated care for the patient while maintaining expertise for each of the two diseases. It is recommended that HIV patients should be tested for TB and vice versa; in addition WHO has published guidelines on cotrimoxazole prophylaxis, provider-initiated testing and counseling of HIV, and antiretroviral treatment, establishing benchmarks for minimum standards of practice. Research is needed to establish new tools for HIV/TB and to optimize use of currently available ones. Population-level interventions should be assessed in highest burden countries such as South Africa. There have been missed opportunities for this during the scale up of ART, and research components of programs rolling out antiretroviral drugs could serve to address questions such as timing of ART initiation and delivery of preventive strategies such as cotrimoxazole and IPT. Prevention of recurrence of TB in HIV-infected patients has emerged as an important research question. Finally, there are serious implications of MDR/XDR-TB on the HIV epidemic in Africa, including exposure of health care workers to incurable TB, that urgently require strengthening of health care systems and laboratory capacity.

UNAIDS, The Joint United Nations Programme on HIV/AIDS

The experience of *UNAIDS* with civil society activism for HIV/AIDS lends itself to the creation of a similar movement to advocate for HIV/TB, given the stark differences between the two diseases in the availability of modern diagnostic tests and treatments, and in funding levels for research. Advocacy is seen as essential to demand more TB research, as the current level of research is insufficient to yield an appropriate response reflecting the urgency of the global TB problem. UNAIDS has called on all its member states to invest more in TB.

EMBARGOED UNTIL NOV 2

WHAT OPPORTUNITIES EXIST TO RAPIDLY ADDRESS URGENT ISSUES IN HIV-TB COINFECTION?

While potential opportunities abound within existing research programs to address the unanswered questions regarding HIV/TB, all of these programs lack either the funding or technical support needed to take advantage of these. This is true for HIV research networks for treatment and prevention and observational cohort studies. There are additional opportunities to conduct operational research that have also not been utilized.

HIV treatment research networks

There are several large HIV treatment research networks conducting studies internationally, such as the NIH-funded trial networks (ACTG, IMPAACT) and ANRS among others. These networks have longstanding expertise in the treatment and management of HIV and opportunistic infections. Allocated resources for these networks are typically limited and already overextended, but these network organizations could be key to advancing some of the urgent research questions in HIV/TB.

The large numbers of HIV-infected individuals in high prevalence settings that are encountered and screened in many of the ongoing studies lend themselves to addressing problems such as diagnostic testing; similarly the field of infection control is one that is relevant to any clinical site in high-burden regions. New collaborations could be established between these networks and other sponsors and organizations to study new drugs, pharmacokinetic interactions or diagnostic tools. The rate limiting factor in the adoption of new approaches in collecting data on HIV-TB coinfection is the dearth of quality controlled TB laboratories in the majority of settings, which require significant funding to establish, with a need to train and retain appropriate human resources.

HIV prevention research networks

While the treatment research networks have begun to incorporate TB into their agendas, the prevention networks (e.g. HVTN, HPTN, MTN) have, as a rule, not yet targeted TB in their programs. However, networks conducting HIV prevention research can play a significant role in contributing to new data on TB diagnosis and prevention, as they screen large number of individuals in high-burden settings. Vaccine trials in particular prospectively collect and store blood specimens that could also be used to determine incidence of TB. One large HIV vaccine trial underway in South Africa has indeed integrated TB screening into study procedures. Overall, barriers include limited resources and the fact sites may not be equipped to screen for TB, in addition to being overwhelmed with the logistical challenges of dealing with voluntary counseling and testing (VCT) of large numbers of people. Symptomatic volunteers are typically

referred to other providers. However, there is a lot of potential to exploit the overlap and synergy between HIV and TB at such research sites, and such efforts should be encouraged and funded.

Cohort studies

Outside of clinical trials networks, observational cohort studies present the potential to answer some of the HIV/TB research questions that have not been addressed by or are not feasible to answer in prospective, randomized clinical trials in the near future. The International epidemiologic Databases to Evaluate AIDS (IeDEA) is an initiative seeking to collect existing data from cohorts around the world to address high priority HIV research questions. The composite cohort network currently contains approximately half a million HIV-infected adults and children, including four African regions (West, Central, East and Southern Africa); Asia and Australia; the Caribbean, Central and South America; North America and Canada.

The consortium includes a TB working group that has identified questions that can be addressed from the data available. These include determining the optimal duration of TB treatment, comparing six versus nine months; TB relapse risk with early versus delayed HAART; the optimal intermittency of TB treatment comparing twice and thrice weekly; and the effect of IRIS on risk of relapse. The database is currently limited by the type of data already collected; taking the example of resistance and DST, available data will be few, as this test is not routinely performed at many sites. Sites have now been asked to provide information on specific TB endpoints that are available. However, there is immense potential to obtain important data from these cohort studies, provided the projects are adequately funded as the project moves forward.

Operational research

The Global Fund represents a mechanism through which countries can conduct operational research, although many opportunities for this have been lost so far, for example to screen for latent TB in prevention of mother-to-child-transmission programs. The Sydney Declaration endorsed by over 1800 delegates at the Sydney IAS Conference in Australia provided a fitting backdrop to these discussions on HIV/TB. However, its call for 10 percent of resources to be allocated to HIV programs to fund research to further improve these programs was not supported by all, as some opposed the idea of diverting funding from life-saving HIV treatment programs.

Other challenges faced in planning operational research within the Global Fund mechanisms include the fact that the country coordinating mechanism (CCM) of proposal submission may be difficult for researchers to access, and conversely, that research expertise within the applicant groups is lacking. Additional technical support could serve to map out existing opportunities to answer operational research questions.

A suggestion was made to consider a specialist review of Global Fund and PEPFAR proposals and country operational plans for this purpose.

Case example of TB screening in HIV prevention research

BANGKOK MSM COHORT STUDY [PERSONAL COMMUNICATION, F. VAN GRIENSVEN & J. VARMA]

The US Center for Disease Control (CDC) is supporting a clinic for men who have sex with men (MSM) in Bangkok that provides screening for HIV and HIV-related care, and is a site for HIV prevention research. First follow up data presented in Sydney from the HIV cohort being established at this site shows that 850 men were screened in the clinic between April 2006 and July 2007 [25]. The CDC investigators Frits van Griensven and Jay Varma have provided a brief description of the TB screening that has recently been incorporated at this site.

A TB screening tool was developed and administered to all patients testing positive for HIV infection; some of the questions were previously validated in HIV-infected populations. Patients are first screened for TB related symptoms. If any symptoms are present, a TB diagnostic evaluation follows that consists of sputum smears and chest X-ray; if active TB is diagnosed, patients are referred to TB treatment elsewhere. In the absence of symptoms, or negative TB diagnostic evaluation, tuberculin skin testing (TST) is performed; patients with positive results are offered IPT.

The major challenge that has been encountered is diagnostic testing, as elsewhere. Sputum collection is challenging, because some patients have difficulty producing sputum and collection must occur over at minimum of 2 days with timely delivery to the hospital laboratory on the same day; yet, routine smear-microscopy for acid-fast bacilli performs poorly in HIV-infected patients. TST is also presents a challenge. With wide variations in sensitivity and specificity, it is difficult to apply and requires another follow up visit within 48 hours. Application may be delayed particularly in this setting where patients to be tested have just learned of their HIV diagnosis and may not be ready for the next battery of tests.

The researchers concur that engagement is needed from as many research communities as possible to look at issues of TB, particularly as they relate to HIV-infected persons. A multi-country study in Thailand, Cambodia and Vietnam is currently underway to develop a simple screening algorithm for TB in HIV-infected patients. The burden of disease is too great for the various research, program and activist communities not to work together to improve diagnosis and care for HIV-patients with TB.

NEXT STEPS

These meetings have successfully identified opportunities for collaboration between the fields of HIV and TB research. There was a strong consensus among meeting participants that the discussions lead rapidly to tangible changes in the landscape of HIV/TB research and its support.

To maintain and act on the momentum from the discussions in these meetings, several suggestions for next steps are listed here:

- The Forum and The TB/HIV Working Group of the Stop TB Partnership seek funding to sponsor meetings at CROI, IAS and other conferences where networking can continue and follow-up of activities reviewed
- Meeting participants with expertise in laboratory procedures propose quality control guidelines for assessment of AFB smear and TB culture and susceptibilities for research studies
 - The development of an informal or formal network of reference TB laboratories for research, and funding needed to develop this would be included in discussions of this group
- The newly revised guidelines on TB infection Control (WHO/CDC) be reviewed and disseminated to research groups for utility at research sites
- Standard guidelines for TB screening (WHO) be developed and disseminated to research groups for screening research participants in HIV studies
- The group organizes a scientific meeting on HIV/TB in occur in conjunction with the next IAS pathogenesis conference in Cape Town, South Africa in 2009

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APPENDIX B: SYMPOSIUM AGENDA

HIV-TB Co-Infection: Meeting the Challenge
July 22, 2007

Chairs: Diane Havlir, Soumya Swaminathan

- 12:30-12:40 Research Priorities in HIV/TB
Stephen Lawn (South Africa)
- 12:40-12:50 MDR-XDR TB
Gerald Friedland (USA)
- 12:50-13:00 Pediatric populations: what is the research agenda?
Mark Cotton (South Africa)
- 13:00-13:10 Update on current & planned clinical trials: where is the momentum?
F. Xavier Blanc (France)
- 13:10-14:30 Panel discussion: agencies and sponsors will highlight how their programs provide opportunities to support and/or fund research to address the gaps identified during the previous talks. Panelists include:
- | | |
|-------------------------------|------------------------|
| Michel Kazatchkine (GRATM) | Michel Sidibe (UNAIDS) |
| Debrework Zewdie (World Bank) | Kevin DeCock (WHO) |
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