

Integrating the care of HIV and TB in developing countries

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National TB programs (NTP) in countries with high HIV prevalence have been confronted with increased TB case loads. The complexity of management of TB has been complicated by smear-negative extrapulmonary disease, high mortality and an association with drug-resistant TB. As a result of international funding, access to antiretroviral therapy (ART) has rapidly expanded. NTP and HIV/ART programs have developed separately and HIV/TB patients receive care in two programs, resulting in duplication of care, and missed treatment opportunities. Collaboration between the services has been successfully demonstrated at strategic levels, national surveillance and in small pilot projects at hospital and clinic level. However, streamlining of services alone will not restore TB control in high HIV prevalence settings. HIV/TB control will require both expanded TB program capacity to detect and treat TB cases earlier in order to decrease the infective pool, and HIV services will need to expand ART coverage to decrease the large pool of susceptible individuals in the population.

The HIV epidemic was first recognized in the early 1980s at a time when TB control was a decreasing priority in developed countries. The resultant reversal of the decades of declining TB incidence in the USA and a worsening burden of TB in developing countries [1] led to an increased international prioritization of TB control. The WHO directly observed short-course therapy strategy (DOTS) was introduced in 1994 and the first Global Plan to Stop TB initiated in 2001 [2]. The Global Plan emphasized access to good-quality, inexpensive TB drugs, together with technical assistance to strengthen existing national TB control programs [3,4]. Between 1990 and 2004, global TB prevalence decreased from 297 to 229 per 100,000. However, TB incidence continued to rise in those countries most heavily affected by the HIV epidemic [5]. The burden of HIV-associated TB is considerably higher than would occur by overlapping of separate noninteracting epidemics. This interaction was manifested by an increased prevalence of HIV amongst those with active TB disease relative to the general population. In high-TB-burden countries, with greater than 5% adult HIV prevalence, the major proportion of TB (51–57%) is HIV related (Table 1) [4,101]. While the HIV epidemic has been associated with increased TB rates of smear-positive pulmonary disease, the HIV-attributable fractions of the more difficult to diagnose smear-negative and extrapulmonary TB disease are markedly higher [6]. HIV/TB is also characterized by a

four- to six-fold increased case fatality during TB therapy [6–8], which is even higher in those with smear-negative disease [6]. The burden of HIV/TB disease has been further worsened by increased rates of TB recurrence following standard TB chemotherapy in HIV-infected individuals [7,8].

Mycobacterium tuberculosis drug resistance to the standard chemotherapeutic agents, rifampicin and isoniazid, is widespread. However, the highest prevalences are in low- and middle-income countries [9]. Up to 10% of multidrug resistance (MDR) cases are infected with extensively drug-resistant strains (XDR) that have additional resistance to fluorquinolone and an injectable second-line drug. XDR existence is a reflection of existing weaknesses in TB control programs [10]. Explosive epidemics of primary MDR and XDR infections have been reported amongst HIV-infected patients [11,12].

The HIV/AIDS epidemic has therefore fuelled TB in areas with highest *M. tuberculosis* transmission. A total of twelve of the 22 highest TB-burdened countries have a general adult population HIV prevalence of greater than 1% (Table 1) [5,101]. HIV has further strained national TB control programs by increasing the total number of TB cases needing treatment, together with an additional complexity of diagnosis and management of smear-negative, extrapulmonary and drug-resistant TB, all of which are associated with high mortality and comorbidity. Although the association between HIV and TB has been

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Table 1. TB burden, HIV seroprevalence in general population and TB patients, and national collaborative strategies for HIV and TB testing.

Country	Population (n)	TB incidence per 100,000	HIV prevalence (%)	HIV% in TB	HIV testing of TB cases	TB testing of HIV cases
India	1,103,371	168 (107–228)	0.9 (0.5–1.5)	22	In specific groups	Yes
China	1,315,844	100 (70–130)	0.1 (<0.2)	Unk	No	No
Indonesia	222,781	239 (154–330)	0.1 (0.1–0.2)	Unk	No	No
Nigeria	131,530	283 (147–421)	3.9 (2.3–5.6)	18	Yes	No
Bangladesh	141,822	227 (165–294)	0.1 (<0.2)	0	No	No
Pakistan	157,935	181 (122–246)	0.1 (0.1–0.2)	0	No	No
South Africa	47,432	600 (501–720)	18.8 (16.8–20.7)	52	Yes	No
Ethiopia	77,431	341 (277–422)	(0.9–3.5)	41	Yes	No
Phillipines	83,054	291 (79–140)	<0.1 (<0.2)	Unk	No	No
Kenya	34,256	641 (490–806)	6.1 (5.2–7.0)	57	Yes	Yes
DR Congo	57,549	356 (262–462)	3.2 (1.8–4.9)	20	Yes	No
Russia	143,202	119 (102–138)	1.1 (0.7–1.8)	Unk	Yes	Yes
Vietnam	84,238	175 (102–253)	0.5 (0.3–0.9)	Unk	No	No
Tanzania	38,329	342 (269–416)	6.6 (5.8–7.2)	51	No	-
Brazil	186,405	60 (54–73)	0.5 (0.3–1.6)	14	Yes	Yes
Uganda	28,816	369 (295–452)	6.7 (5.7–7.6)	51	Yes	Yes
Thailand	64,233	142 (93–204)	1.4 (0.7–2.1)	Unk	In specific groups	No
Mozambique	19,792	447 (357–544)	16.1 (12.5–20.0)	Unk	No	No
Myanmar	50,519	171 (98–246)	1.3 (0.7–2.0)	Unk	No	Yes
Zimbabwe	13,010	601 (491–729)	20.1 (13.3–27.6)	Unk	-	-
Cambodia	14,071	506 (335–686)	1.6 (0.9–2.6)	8.2	Yes	Yes
Afghanistan	29,863	168 (105–229)	0.1 (<0.2)	Unk	No	-

The 22 countries with the highest global TB burden.

Data taken from [5,6].

known almost since the start of the HIV epidemic, programs to implement collaborative TB/HIV activities in resource-poor countries have been developed only in the past 5 years. With the increasing availability of antiretroviral drugs, the number of countries that have policies to implement collaborative TB/HIV activities is increasing rapidly. The Global Plan to STOP TB, 2006–2015 outlines a framework together with ambitious targets for global TB control. However, the plan acknowledges that these targets are unlikely to be achieved in Eastern Europe and Africa owing to the complexity of managing MDR-TB and HIV/TB coinfection [4]. This review will address the organization of TB and HIV services within a conceptual framework of TB/HIV interactions.

Barriers to integration of HIV & TB services

Two separate disease-management structures have developed with different characteristics and very divergent philosophies. National TB programs (NTP)s have developed over decades, using a centrally organized public-health approach. Treatment is strongly tied to population control of TB transmission, concentrating on standardized diagnosis and chemotherapy of self-referring individuals with predominantly smear-positive pulmonary TB. NTPs have developed pragmatic targets for DOTS coverage, cure rates (>80%) and case finding (70% of smear-positive disease). Medication is typically dispensed daily under direct supervision for a period of 6–9 months, and is

usually given at a community level of care. NTPs have successfully made complex TB treatment scalable and effective.

By contrast, HIV services have developed more recently and are patient-orientated, with a strong emphasis on human rights and social justice. Individual HIV management is weakly linked to epidemic disease control, as many HIV-infected individuals are unaware of their status and are not in care. Antiretroviral therapy (ART) availability in developing countries has increased markedly since 2002 as a result of international funding efforts such as the Global Fund to Fight AIDS, Tuberculosis and Malaria [102] and the Presidents Emergency Program for AIDS Relief [103]. The rapidity of roll out of ART in many African countries has resulted in development of ART and HIV care at district levels, where suitable pharmacy and clinical expertise were already available. In developing countries, patients typically enter ART programs with very advanced disease and low CD4 cell counts [13,14], when they are vulnerable to a wide spectrum of opportunistic infections including TB [15,16]. ART is a life-long requirement and medication is usually dispensed monthly. However, ART is only one component of the required package of HIV care, as there is a need for diagnosis and treatment of a disparate array of opportunistic infections and neoplasms, end-of-life and palliative care, together with nutritional and social support and the promotion of safe behaviors. HIV/TB management is further complicated by the need to access medication at both community and district levels.

Rationale for integration of TB & HIV services

TB and HIV are intimately intertwined at both an individual and epidemic level. The burden of HIV/TB disease on both TB and HIV care services has been particularly high in developing countries. Large and rapidly growing numbers of patients with HIV and TB coinfection require coordinated diagnosis, care and treatment. HIV/TB cases receive care in two separate public-health systems, resulting in duplication of patient–health provider interactions, and the lack of integration between the services results in missed opportunities for prevention and prophylaxis. TB services focus predominantly on smear-positive pulmonary disease, with the result that HIV-positive patients with smear-negative pulmonary TB or

extrapulmonary disease can be repeatedly referred between HIV and TB services, resulting in delayed diagnosis, loss to service or even death [17].

Proposals for integration of TB and HIV services have stressed the need for harmonization of policies and planning at a strategic level, including adaptation of surveillance tools to incorporate both TB and HIV information in HIV and TB registers. National programs have explored the adaptation of the existing separate services to include the needs of HIV/TB, particularly focusing on introducing testing and screening for both conditions in each service, together with facilitation of referrals between services. Full integration to develop a ‘one-stop shop’ for HIV/TB cases has not been widely advocated; however, such a strategy has been explored in pilot studies [17].

WHO interim recommendations for HIV/TB integration

Large and rapidly growing numbers of patients with TB and HIV coinfection require coordinated systems for diagnosis, management and surveillance of HIV/TB. Collaboration and harmonization between national TB and HIV programs, together with some degree of integration of services at local level, have been advocated by the WHO.

The WHO has recommended that countries (category I) or districts within countries (category II) that have more than 1% general adult HIV prevalence enact specific HIV/TB coordinated initiatives [104]. Recommended collaborative activities are focused on three main areas:

- Establishing HIV/TB coordinating bodies for planning, surveillance and monitoring
- Decreasing the burden of TB in people living with HIV/AIDS by intensified case finding, isoniazid preventive therapy and infection control in public places
- Decreasing the burden of HIV amongst those with TB by provision of HIV testing and counseling as an entry to care and support services, including cotrimoxazole preventative therapy (CPT) and ART.

Specific global targets were that by 2005, all category I and II countries should have established national coordinating bodies, and that by 2007 they should have developed joint TB/HIV implementation plans and have established HIV surveillance among TB patients [104].

Coordination of national TB & HIV control programs

National coordination of TB and HIV activities allows for implementation of national surveillance and reporting of both HIV status in TB registers and treatment records and reporting of TB screening within HIV registers. In 2005, of 63 TB/HIV focus countries, 60 provided data to the WHO indicating that the majority (58–71%) had developed national plans and policies for testing all TB patients for HIV and policies for provision of CPT and ART. However, only 34–41% had policies on intensified TB case finding, IPT provision and infection control among HIV-infected individuals [18]. By 2006, of 22 countries with the highest TB burdens, nine (41%) reported to the WHO that they had instituted national HIV/TB coordinating plans that included universal testing for HIV among patients presenting to the TB programs (Table 1) [5,6]. Of the 12 countries with high TB burden together with a general population HIV prevalence of more than 1%, nine (75%) had instituted universal testing for HIV infection in TB cases. The number of countries with national plans for universal screening for TB among HIV cases was seven (32%) and five (42%) of the 22 high-TB burden countries and 12 high-HIV and TB burdens, respectively (Table 1) [4,6].

Integration of TB diagnosis into counseling & testing services

The ProTEST initiative was established in 1997 by the WHO to explore collaboration between HIV/AIDS and TB control programs within six pilot projects in high HIV prevalence settings in Malawi, South Africa and Zambia [19,20]. Voluntary counseling and testing (VCT) was the entry point to all interventions, and by 2004 more than 140,000 people accessed VCT for HIV within these projects. Monitoring and evaluation of the projects did not use standardized definitions, making direct comparisons difficult. All projects introduced enhanced HIV prevention strategies; however, the impact of these interventions was not measured. Although the provision of isoniazid and cotrimoxazole preventive therapies was shown to be feasible within these collaborative TB/HIV projects, the uptake of preventive therapy among eligible clients was low. Symptomatic screening for TB in VCT centers, using administration of a symptoms questionnaire, was found to be easy to implement at little additional cost. Active TB was identified on the presence of symptoms in 1–10% of those testing HIV positive [20].

Integration of HIV testing into TB programs

The WHO has reported that TB and HIV/AIDS control programs in most countries have begun to respond to the challenge of HIV/TB [18]. However, the majority of countries do not yet have universal HIV testing within TB control programs and low rates of HIV testing are, in most countries, currently the principal obstacle to providing ART to TB patients. The coverage of these services in 2005 was far less than anticipated by the Global Plan in 2006, the first year of its implementation.

Examples of national programs to increase HIV testing among TB cases have been reported from African countries. In 2004, Rwandan health workers who diagnose TB were trained to test confirmed TB cases for HIV infection [21,22]. TB monitoring and recording forms were also modified to include TB/HIV data. HIV testing of TB cases was reported to increase from 46% of TB patients in 2004 to 81% by the third quarter of 2006. In 2005, health staff working in district hospitals or clinics of the Kenyan TB control program underwent training to perform HIV testing and institute CPT [23]. The national TB register was adapted to capture HIV/TB data, and HIV testing was reported to have increased among TB cases from 32% in 2005 to 64% by the third quarter of 2006. In Zambia, during 2006, all district and clinic staff were trained in implementation of national HIV testing and counseling guidelines [22]. TB monitoring and recording forms were modified to capture TB/HIV data. Patients were referred to ART clinics for CPT. Reported HIV testing in the Southern Province increased from 2% in 2005 to 52% in the third quarter of 2006 [22].

Integration of TB management into HIV home-based care

A report on the introduction of DOTS TB care into an established non-governmental organization (NGO) organized home-based care program in 1998 and 1999, during the pre-ART era in Zambia, illustrated both the potential for integration at this level of care, together with a highlighting of some of the difficulties in achieving and evaluating outcomes of such an intervention [23]. The intervention consisted of daily home visits to HIV/TB-infected individuals for DOTS during the intensive phase of therapy, with a similar comparator population managed at a local TB clinic of the NTP. Recent changes to the NTP made prior to the study period made

historical comparisons invalid and the comparator clinic performance varied during the 2 years of the study. High mortality (>20%) at both sites also made conventional NTP targets nonachievable and the restriction of treatment outcomes to only smear-positive cases decreased the relevance for HIV-infected smear-negative and extrapulmonary TB. With extra training, DOTS was able to be incorporated into home-based care but because of the stigma associated with HIV-related home visits, some patients preferred to continue daily visits to the TB clinic [23].

Program collaboration strategies for treatment of HIV/TB

There is broad consensus that integration between the TB and HIV programs is desirable to rationalize the care of those with, or at risk of, dual infection [4]. However, the degree of possible integration will depend on factors such as differing HIV and TB prevalences, the configuration of existing services, available resources and the ability and willingness of services to adapt. Therefore, there is a spectrum of possible integrative strategies, ranging from maintenance of two separate programs, with enabling of cross-referrals between services, to full integration, resulting in a single 'one-stop shop'. Between these two extremes, some mixing of program responsibilities will result in delivery of TB services that address HIV needs and HIV services that address TB care.

Collaboration between separate HIV & TB programs

Malawi is an example of a country with high burdens of HIV and TB which has maintained separate TB and HIV programs [24,25]. Malawi has a population of 12.9 million with more than 76% living on less than US\$2 a day and a per-capita expenditure on health of US\$16 dollars per annum. There was a fivefold rise in TB notifications between 1985 and 2000 to an incidence rate of greater than 200/100,000 (27,000 notified cases per annum), of whom 77% are HIV coinfecting. The NTB program is based on WHO-recommended DOTS treatment with its own directorate, with central, regional and district tiers responsible for TB control. Case management is by health assistants, working within the 44 hospitals treating TB within the general health service. TB surveillance now incorporates HIV testing data entered into the register by a district TB officer. TB officers are health assistants with little

clinical training and are not qualified to manage other diseases. HIV testing and cotrimoxazole prophylaxis phased introduction into the TB service was part of a 2003–2005 TB/HIV plan. In 2005, 47% of TB cases had been tested for HIV, and of the 69% testing HIV positive, 90% started cotrimoxazole.

Nationally, there are close to a million HIV-infected individuals (480,000 to 1.4 million) of whom 170,000 are in immediate need of ART. HIV counseling and testing and HIV management are provided by a separate program managed by the Department of Clinical Services. Within this HIV service there has been a rapid expansion of ART provision. In January 2004, nine facilities provided ART to 3000–4000 patients, which was approximately 2.4% of the estimated need. By July 2005, 30,055 patients had started ART in 60 centers using a standardized approach delivered by clinical officers. A fixed-dose combination of nevirapine/stavudine/lamivudine is used by the program. Patients with TB coinfection delay start of ART for the first 2 months of TB therapy because of possible drug–drug interactions. ART is subsequently started when the TB continuation phase of isoniazid and ethambutol is commenced. Mycobacterial culture and drug-sensitivity testing are not performed routinely and the efficacy of this regimen for HIV/TB and has not been fully characterized. HIV/TB cases can attend the same hospital on the same day but are required to queue separately for each service.

Integration of HIV/TB treatment & care

A pilot project in Durban, South Africa, gives an example of integration of ART and TB disease management in an urban setting. The project is based in a public municipal TB clinic with a case load in excess of 11,000 new cases of TB per annum. Directly observed TB therapy is provided on site or via a variety in local community-care settings. Concomitant DOT ART and TB were instituted for coinfecting patients using once-daily ART during 6–9 months of TB treatment, followed by referral to hospital-based ART care subsequently. Early results demonstrate reasonable on-treatment antiretroviral CD4 and viral suppression results [25].

A similar strategy has been explored in Tugela Ferry, at a district hospital serving 300,000 traditional Zulu people in rural KwaZulu-Natal (KZN) [25]. This area suffers some of the highest HIV and TB rates in South Africa, with a poorly

performing TB control program, manifested by low treatment-completion rates (59%). In 2001, an HIV clinic was established that provided cotrimoxazole prophylaxis and home-based palliative care. An ART program was introduced, and doctors, nurses and community workers received training in HIV management. During their monthly hospital visit, TB/HIV patients construct, under supervision, a months' supply of medication to be taken once-daily at home. Adherence is supported by family members and community treatment workers. After 12 months, TB completion rates improved from 59 to 83%. Of concern, a high death rate amongst dually infected patients was found to be due to a high prevalence of a resistant strain of *M. tuberculosis*, which appeared to have been acquired by recent nosocomial or community transmission [11].

Full integration of TB and HIV programs at a local clinic level has been explored in the Khayelitsha health district of Cape Town, South Africa [20,25]. In 2000, HIV/AIDS clinics were established in close proximity to the local TB services of the South African NTP. In 2001, ART was added to the HIV clinic service, which steadily expanded to deliver ART to 1400 individuals by September 2005. In 2003, a policy of stepwise integration of the two services within the same building was initiated using a common reception area. Administration and staff management was shared, and increased training of each service's staff in the other service's procedures was initiated. Integration of staff from the two services necessitated collaboration between five different employing agencies. A uniform patient-centered approach was encouraged, using shared medical folders incorporating both HIV and TB medical records. During 2003, early assessment of the program reported HIV testing at TB clinic entry to be 22%, increasing to 54% at the completion of TB treatment. TB diagnosis was modified from a reliance only on sputum smear by the addition of mycobacterial culture allowing development of an algorithm for diagnosis of HIV-infected patients with smear-negative TB. The simplified care pathways demonstrated the potential for service-level integration, but case loads were reported to be extremely high, resulting in an urgent need for a more streamlined clinic building and improved management capacity.

Infection control

Concerns have been expressed that integration of TB and HIV services could result in increased

mixing of TB-infectious and TB-vulnerable patients with advanced HIV infection, leading to worsening of infection control in resource-poor settings [26,27]. A large outbreak of XDR-TB in rural South Africa, associated with rapid and nearly universal mortality among HIV patients receiving standard TB therapy and antiretrovirals, has highlighted the serious consequences of healthcare-associated transmission, which may have resulted from breakdown of institutional infection control [11].

The cornerstone of infection control in both integrated and nonintegrated programs is the combination of efficient case management, together with minimizing of environment contamination. Efficient case management incorporates the early recognition, rapid diagnosis and speedy institution of appropriate antimycobacterial therapy with ongoing monitoring of response to treatment to identify early development of resistant strains of TB. Without adequate diagnostics, however, cases of TB go unrecognized and remain as sources for subsequent nosocomial transmission. Calls have been made for expanded program capacity including an expanded global access to sputum culture and drug-sensitivity testing [26]. Meanwhile, integrated programs require the development of a system-wide approach to infection control, including optimized TB case management, segregation of active cases, and encouragement of cough hygiene, together with environmental measures. In resource-poor settings, technologies such as positive-pressure air conditioning, ultraviolet air cleansing and individual respiratory protective devices are unavailable. Environmental control relies on less technically intensive measures, such as separate scheduling of potentially infected patients, cough hygiene, the safe handling of infectious sputum, natural ventilation and the performance of high-risk procedures, such as sputum induction in the outdoors [28].

Discussion

Integration of services at a national strategic planning level has proved achievable. Although TB and ART programs have very different characteristics, most high-burden countries have successfully set up national bodies to coordinate collaboration between the services. A major achievement has been the harmonization of monitoring of HIV/TB by incorporation of information on both diseases in HIV and TB registers in some countries. However, recording

Executive summary**Barriers to integration of HIV & TB services**

- National TB services
 - Well established
 - Centrally organized
 - Treatment 6–9 months
 - Treatment and disease control closely linked
- HIV services
 - Rapidly expanding
 - Patient oriented
 - Lifelong treatment
 - Treatment not closely linked to disease control

Rationale for integration of TB & HIV services

- Strong epidemiologic linkage between diseases.
- Patients require care in two services.
- TB diagnosis portal to HIV care.
- HIV/AIDS complicates management of TB.

WHO interim recommendations for HIV/TB integration

- Specific HIV/TB collaborative activities required if HIV prevalence is more than 1%.
- Establishment of national coordinating bodies by 2007.
- Initiate measures to decrease burden of TB in people living with AIDS.
- Initiate measures to decrease burden of HIV in those with TB.

Coordination of national TB & HIV control programs

- In 2005, 57–71% of HIV/TB focus countries had implemented policies for HIV testing and provision of cotrimoxazole preventive treatment in TB programs.
- In 2005, only 34–41% had implemented policies for intensified TB case finding and isoniazid preventive therapy (IPT) in HIV services.

Integration of TB diagnosis into counseling & testing services

- ProTEST initiative in Malawi, Zambia and South Africa explored voluntary counseling and testing as entry into HIV/TB care.
- By 2004, 140,000 voluntary counseling and testings had been performed.
- Symptoms questionnaire identified 1–10% active TB in those testing HIV positive.

Integration of HIV testing into TB program

- Less than 50% of highest-TB-burden countries have instituted universal HIV testing in a TB program.
- Training of TB officers in voluntary counseling and HIV testing (VCT) in Rwanda and Zambia was followed by a doubling in the rate of HIV testing in TB programs.

Integration of TB diagnosis into HIV home-base care

- Directly observed short-course therapy strategy TB can be incorporated into home-based care program.
- Home visits by HIV service staff may be resented owing to stigma.

Program collaboration strategies for treatment of HIV/TB

- Model of collaboration between separate HIV and TB programs.
- Model of adaptation of both TB and HIV services to meet needs of coinfecting patients.
- Model of full integration of HIV/TB treatment and care.

Infection control

- Epidemic of extensively drug-resistant strains in rural populations highlighted concerns of nosocomial spread of TB following mixing of infectious TB cases with highly susceptible individuals.
- Infection control dependent on efficient case management, but environmental and respiratory protection measures are frequently lacking in resource-poor settings.
- There is an urgent need for increased access to mycobacterial culture and drug-sensitivity monitoring.

Executive summary (cont.)**Discussion**

- HIV/TB integration at national planning level has been demonstrated.
- Surveillance of HIV/TB in high-burden countries is improving:
 - Integration of services alone in high-burden countries is unlikely to restore TB population control
 - HIV/TB case management requires increased access to diagnostics and adaptation of existing programs
 - Patients in resource-poor settings access antiretroviral therapy at very low CD4 cell counts
 - Wide access to voluntary counseling and testing and longitudinal HIV care will allow initiation of antiretroviral therapy at higher CD4 cell counts and reduced HIV/TB case load

and reporting remains weak and many of the countries that have collaborative TB/HIV activities are unable to report fully on recommended indicators [18]. A further challenge for NTPs is how to adapt TB control to the needs of HIV-infected, while maintaining the successes of TB programs that have been demonstrated in HIV-negative populations. Once diagnosed, the treatment of TB in both HIV-infected and non-infected has remained standardized. The NTP reliance on passive case finding, sputum smear and existing DOTS targets are, however, less relevant for coinfecting patients. Symptoms screening has been successfully incorporated into VCT programs at a low cost per case detected. Increased access to ART has resulted in large numbers of HIV-infected individuals presenting for care in resource-constrained settings. The majority of these patients present with advanced immune suppression when mortality is high and there is an urgent need for access to ART and a spectrum of other diagnostic and preventative services, which are novel to the staff of the NTP. HIV/TB with advanced immune suppression is ill-suited for diagnosis in either of the presently configured NTP or ART roll-out programs. Further adaptation of existing programs is necessary to increase access to culture or other TB diagnostic modalities.

The challenge of HIV/TB to the ART program is its protean clinical manifestations that can mimic other opportunistic infections (OIs), together with a lack of a sensitive point-of-care diagnostic test. HIV/TB, especially multidrug resistance and extensively drug-resistant strains, have also exposed the lack of infection-control measures in African health facilities.

While integration of existing TB and HIV treatment services may streamline health systems, reduce referral delays and improve individual case management, the integration of these services alone is unlikely to be sufficient to control TB at a population level. HIV/TB complicates and delays the initiation of ART in

patients with advanced immune suppression. Early initiation of ART soon after a TB diagnosis may result in drug–drug interactions, precipitate immune restoration disease and result in an increased pill burden [29]. However, delay in initiation may be associated with high HIV mortality, especially in those with low CD4 cell counts [30]. These advantages and constraints to early treatment of coinfecting patients are made more acute because patients are presenting at much lower CD4 cell counts in resource-poor compared with industrialized countries [13,14]. Earlier initiation of ART, at CD4 cell counts closer to the guideline threshold of 200 cells/mm, will add to ART program case-load, but this strategy may result in a decreased TB case-load [3]. Program changes will be required that emphasize earlier identification of HIV-infected individuals, prior to development of symptoms associated with advanced immune suppression including HIV/TB, with subsequent access to monitoring of HIV progression together with ongoing active TB case finding.

Conclusion

The HIV epidemic is undermining TB control in many high TB burden countries. Increasing numbers of co-infected patients have resulted in limited collaboration between HIV and TB programs at different levels of the healthcare system. HIV testing of TB cases currently provides a major portal for entry into HIV care however; HIV testing is still far from universal within TB programs. Advanced HIV disease makes TB a diagnostic challenge, requiring increased access to diagnostic modalities additional to sputum smear. Earlier access to HIV care including screening for TB screening will also require expansion and reconfiguration of HIV services.

Future perspective

Collaboration between the existing TB and HIV programs will increase. However, there will continue to be a need for expanded access to HIV

counseling and testing outside of these programs. Increased identification of HIV infection at earlier stages of disease progression will result in a need for the development of models of longitudinal HIV care. Such programs will incorporate ongoing TB disease screening, allowing diagnosis and treatment prior to development of profound immune suppression. The combination of earlier access to care and improved coverage of ART will result in a decrease in the highly TB-susceptible population presently driving the HIV/TB epidemic. Diagnosis of HIV/TB will be enabled by both new diagnostics and a wider access to existing mycobacterial culture, and nucleic acid amplification tests. The increasing recognition of multidrug resistance and extensively drug-resistant strains TB strains will drive the need to more closely monitor response to

therapy and surveillance for mycobacterial resistance within programs. Improved environmental monitoring technologies will allow earlier identification of breakdowns in infection control within busy health facilities and the institution of measures to diminish and monitor nosocomial transmission.

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Bibliography

- WHO: *Global Tuberculosis Control. WHO Report 2000*. WHO, Geneva, Switzerland (WHO document WHO/CDS/TB/2000.275) (2000).
- WHO: *Global Plan to Stop Tuberculosis: Phase 1, 2001–2005*. Geneva, Switzerland (WHO/HTM/STB/2001.16) (2001).
- WHO/Stop TB Partnership: *Sustaining the Gains: National Self-sufficiency For Tb Drug Access: a Global Drug Facility Strategy*. World Health Organization, Geneva, Switzerland (WHO/HTM/STB/2005.34) (2005).
- WHO: *Global Tuberculosis Control: Surveillance, Planning and Financing*. WHO, Geneva, Switzerland (WHO/HTM/STB/2006.362) (2006).
- WHO: *Global Tuberculosis Control: WHO Report 2003*. WHO, Geneva, Switzerland (WHO/HTM/TB2004.331) (2004).
- Connolly C, Reid A, Davies G, Sturm W, McAdam KP, Wilkinson D: Relapse and mortality among HIV-infected and uninfected patients with tuberculosis successfully treated with twice weekly directly observed therapy in rural South Africa. *AIDS* 3(12), 1543–1547 (1999).
- Mukadi YD, Maher D, Harries A: Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 15(2), 143–152 (2001).
- Harries AD, Chimzizi RB, Nyirenda TE, van Gorkom J, Salaniponi FM: Preventing recurrent tuberculosis in high HIV-prevalent areas in sub-Saharan Africa: what are the options for tuberculosis control programs? *Int. J. Tuberc. Lung Dis.* 7, 616–622 (2003).
- Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ *et al.*: Global incidence of multidrug-resistant tuberculosis (2003). *J. Infect. Dis.* 194(4), 479–485 (2006).
- Raviglione MC, Smith IM: XDR tuberculosis implications for global public health. *N. Engl. J. Med.* 356, 656–659 (2007).
- Ghandhi NR, Moll A, Sturm AW *et al.*: Extensively drug resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 368, 1575–1580 (2006).
- Frieden TR, Sherman LF, Maw KL *et al.*: A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical features. *JAMA* 276(15), 1229–1235 (1996).
- Ivers LC, Kendrick D, Doucette K: Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. *Clin. Infect. Dis.* 41(2), 217–224 (2005).
- ARTLINK writing committee: Mortality of HIV-1 patients in the first year of antiretroviral therapy: comparisons between low-income and high-income countries. *Lancet* 367(9513), 817–821 (2006).
- Lawn SD, Myer L, Orrell C, Bekker L-G, Wood R: Early mortality among patients accessing a community-based antiretroviral program in South Africa: implications for program design. *AIDS* 19, 2141–2148 (2005).
- Holmes CB, Wood R, Badri M *et al.*: CD4 decline and incidence of opportunistic infections in Cape Town, South Africa. Implications for prophylaxis and treatment. *J. Acquir. Immune Defic. Syndr.* 42(4), 464–469 (2006).
- Coetzee D, Hilderbrand K, Goemaere E, Matthys F, Boelaert M: Integrating tuberculosis and HIV care in the primary care setting in South Africa. *Trop. Med. Int. Health* 9(6), A11–A15 (2004).
- WHO: *Global Tuberculosis Control: Surveillance, Planning, Financing: WHO Report 2007*. WHO, Geneva, Switzerland (WHO/HTM/TB/2007.376) (2007)
- Godfrey-Faussett P, Maher D, Mukadi YD, Perriens J, Raviglione M: How human immunodeficiency virus voluntary testing can contribute to tuberculosis control. *Bull. WHO* 80(12), 939–945 (2002).
- WHO: Report of a ‘Lessons Learnt’ Workshop on the Six ProTest Pilot Projects in Malawi, South Africa and Zambia: WHO, Geneva, Switzerland. (WHO/HTM/TB/2004.336) (2004).
- Gasana M, Vandebriel G, Kabanda G *et al.*: Tuberculosis in Rwanda: challenges to reaching the targets: *Bull WHO* 85(5), 383–384 (2007).
- WHO: *Scaling Up HIV Testing Among TB Patients: Three Case Studies: Global Tuberculosis Control: Surveillance, Planning, Financing*. WHO report. WHO, Geneva, Switzerland (WHO/HTM/TB/2007.376) (2007).
- Miti S, Mfungwe V, Reijer P, Maher D: Integration of tuberculosis treatment in a community-based home care program for persons living with HIV/AIDS in Ndola, Zambia. *Int. J. Tuberc. Lung Dis.* 7(9), S92–S98 (2003).
- Chimzizi R, Harries A: Joint tuberculosis/HIV services in Malawi: progress, challenges and the way forward. *Bull. WHO* 85(5), 385–386 (2007).

25. Friedland G, Harries A, Coetzee D: Implementation issues in tuberculosis/HIV program collaboration and integration: three case studies. *J. Infect. Dis.* 196(Suppl. 1), S114–S123 (2007).
26. Hamilton CD, Sterling T, Blumberg HM, Leonard M, McAuley J, Schlossberg D: Extensively drug-resistant tuberculosis: are we learning from history or repeating it? *Clin. Infect. Dis.* 45, 338–342 (2007).
27. Wells CD, Cegielski JP, Nelson LJ *et al.*: HIV-infection and multidrug-resistant tuberculosis: the perfect storm. *J. Infect. Dis.* 196(Suppl. 1), S86–S107 (2007).
28. Wood R, Middelkoop K, Myer L *et al.*: The burden of undiagnosed tuberculosis in an African community with high HIV-prevalence: implications for TB control. *Am. J. Resp. Crit. Care Med.* 175(1), 87–93 (2007).
29. Lawn SD, Myer L, Bekker L-G, Wood R: Tuberculosis associated immune reconstitution disease: risk factors and impact in an antiretroviral treatment program in sub-Saharan Africa. *AIDS* 21(3), 335–341 (2007).
30. Lawn SD, Myer L, Harling G, Orrell C, Bekker L-G, Wood R: Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation. *Clin. Inf. Dis.* 43(6), 770–776 (2006).

Website

101. Report on the global AIDS epidemic 2006: UNAIDS, 2006, Geneva, Switzerland. www.unaids.org/en/HIV_data/2006GlobalReport/default.asp
102. The Global Fund to Fight AIDS, Tuberculosis and Malaria. www.theglobalfund.org
103. USA Presidents' Emergency Plan for AIDS Relief: www.pepfar.gov
104. Interim policy on collaborative TB/HIV activities: WHO, Geneva, Switzerland (2004). http://whqlibdoc.who.int/hq/2004/who_htm_tb_2004.330.pdf