INT J TUBERC LUNG DIS 9(3):238–247

Can we get more HIV-positive tuberculosis patients on antiretroviral treatment in a rural district of Malawi?*

R. Zachariah,* R. Teck,† O. Ascurra,† P. Gomani,† M. Manzi,† P. Humblet,* P. Nunn,‡ F. M. L. Salaniponi,§ A. D. Harries¶#

*** Medical Department (HIV-TB Operational Research), Brussels Operational Centre, Médecins sans Frontières, Brussels, Belgium; † Médecins sans Frontières-Luxembourg, Thyolo, Malawi; ‡ STOP-TB Unit, World Health Organization, Geneva, Switzerland; § National Tuberculosis Control Programme and ¶ HIV Care and Support, Ministry of Health and Population, Lilongwe, Malawi; # London School of Hygiene and Tropical Medicine, London, UK**

SUMMARY

The World Health Organization (WHO) has set a target of treating 3 million people with antiretroviral treatment (ART) by 2005. In sub-Saharan Africa, HIV-positive tuberculosis (TB) patients could significantly contribute to this target. ART (stavudine/lamivudine/nevirapine) was initiated in Thyolo district, Malawi, in April 2003, and all HIV-positive TB patients were considered eligible and offered ART. Despite this, only 44 (13%) of 352 TB patients were eventually started on ART by the end of November 2003. Most TB patients leave hospital after 2 weeks to complete the initial phase of anti-tuberculosis treatment (rifampicin-based) in the community, and ART is offered to HIV-positive TB patients after they have started the continuation phase of treatment (isoniazid/ethambutol). ART is only offered at hospital, while the majority of TB patients take their continuation phase of anti-tuberculosis treatment from health centres. HIV-positive TB patients therefore find it difficult to access ART.

In this paper, we discuss a series of options to increase the uptake of ART among HIV-positive TB patients. The main options are: 1) to hospitalise HIV-positive TB patients with a view to starting ART in the continuation phase in hospital; 2) to decentralise ART delivery so ART can be delivered at health centres; 3) to replace nevirapine with efavirenz so ART can be started earlier in the initial phase of anti-tuberculosis treatment. Decentralisation of ART from hospitals to health centres would greatly improve ART access.

KEY WORDS: TB; HIV; Malawi; HAART; rural district

IN SETTINGS of high human immunodeficiency virus (HIV) prevalence, tuberculosis (TB) and HIV programmes have mutual interest in collaborating with each other. HIV infection is fuelling the TB epidemic, and TB continues to be the most common cause of morbidity and mortality in HIV-positive populations.[1,2] TB is often what brings the HIV-positive individual to medical attention, and individuals presenting with TB in high HIV prevalence settings are likely to be co-infected with HIV. The World Health Organization (WHO) has set an ambitious target of treating 3 million people with antiretroviral treatment (ART) by 2005, the so-called '3 by 5' target.[3] As TB patients constitute a readily identifiable group in the health system for HIV testing and ART, they could significantly contribute to this target.

Malawi, a small, resource-poor country in central southern Africa, has an estimated national HIV prevalence rate of 9%, with 900 000 people thought to be HIV-infected.[4] In 2000, a countrywide survey found that 77% of new patients registered with TB were co-infected with HIV.[5] Thyolo district, in rural southern Malawi, has been pioneering joint TB-HIV interventions and ART for HIV-positive eligible patients, including TB patients, in the country. According to the Malawi ART guidelines[6] and WHO guidelines,[3] all HIV-positive individuals in WHO Stage III or IV are eligible for ART. HIV-positive individuals with pulmonary TB (PTB) are classified as WHO Stage III and those with extra-pulmonary TB (EPTB) are classified as WHO Stage IV.

ART (stavudine/lamivudine/nevirapine) was initiated in the main public hospital in Thyolo district (Thyolo District Hospital) on 22 April 2003; by the end of November 2003, 345 HIV-positive individuals had been placed on treatment. Because the initial phase of anti-tuberculosis treatment for new TB patients is rifampicin (R, RMP) based and because of drug interactions between RMP and nevirapine,[3] ART is currently offered to all HIV-positive TB patients only after

Correspondence to: Dr Rony Zachariah, Medical Department (Operational Research HIV-TB), Médecins sans Frontières, Brussels Operational Centre, 68 Rue de Gasperich, L-1617 Luxembourg. Tel: (+352) 332515. Fax: (+352) 335133. e-mail: zachariah@internet.lu

Article submitted 27 January 2004. Final version accepted 17 June 2004.

[A version in French of this article is available from the Editorial Office in Paris and from the Union website www.iuatld.org]

Table 1 Tuberculosis (TB) treatment regimens

Type of TB	Drug regimens and duration*	Comments
New smear-positive PTB and serious EPTB	0.5RHZE/1.5$R_3H_3Z_3E_3$/6EH	Initial phase: Initial 2 weeks daily RHZE in hospital; 6 weeks intermittent RHZE in hospital, under health centre supervision or guardian supervision. Continuation phase: 6 months daily EH
New smear-negative PTB and less serious EPTB	0.5RHZ/1.5$R_3H_3Z_3$/6EH	Initial phase: Initial 2 weeks daily RHZ in hospital; 6 weeks intermittent RHZ in hospital, under health centre supervision or guardian supervision. Continuation phase: 6 months daily EH
Retreatment of smear-positive PTB relapses, failure cases and cases who return after default	2SRHZE/1RHZE/5$R_3H_3Z_3E_3$	Initial phase: 2 months daily SRHZE in hospital; 1 month daily RHZE, usually in hospital. Continuation phase: 5 months intermittent treatment in hospital, health centre or guardian supervision.
TB meningitis in adults and children	2SRHZ/7RH	Initial phase: 2 months daily SRHZ in hospital. Continuation phase: 7 months daily RH in hospital, health centre or guardian supervision.

* A regimen consists of two phases—initial phase and continuation phase. The number before a phase is the duration of that phase in months. A number in subscript after a letter is the number of doses of that drug per week. If there is no number in subscript after a letter, then treatment is daily.
PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis; R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; S = streptomycin.

completing the initial 2 months of anti-tuberculosis treatment (Table 1). During this same period, 352 HIV-positive TB patients had completed this initial phase of anti-tuberculosis treatment and went on to start the continuation phase, consisting of isoniazid (H, INH) and ethambutol (E, EMB). Although all these TB patients were eligible for ART and were informed of the offer, only 44 (13%) were eventually started on ART (Figure 1). This relatively low uptake of ART in HIV-positive TB patients is of concern. The problem is likely to lie within the TB-HIV patient circuit and result from the fact that anti-tuberculosis treatment is largely decentralised,[7] while HAART is centralised and currently available at only one site (Thyolo District Hospital). Is it possible to get more HIV-positive patients with active TB on ART? In this paper, we describe the circuit of a TB patient in terms of TB management and ART in Thyolo District Hospital. We then discuss possible options to try and increase the current uptake of ART in HIV-positive individuals with active TB.

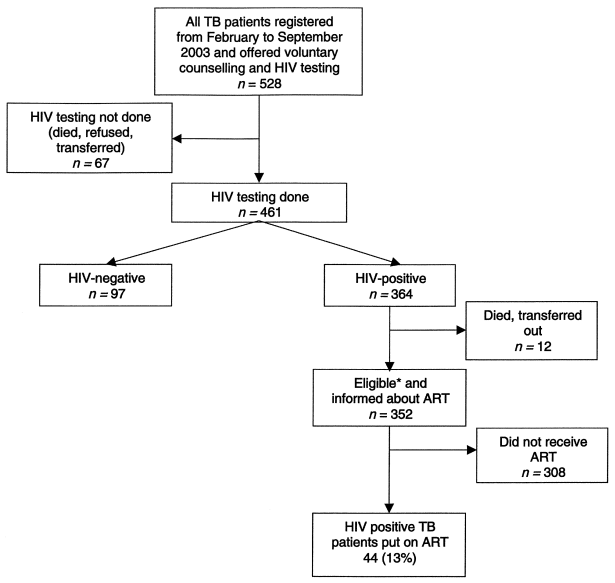

Figure 1 Uptake of ART among HIV-positive tuberculosis (TB) patients in Thyolo, Malawi. *Individuals who had completed their initial phase (2 months) of anti-tuberculosis treatment and were supposed to start ART during the period April to November 2003. VCT = voluntary counselling and HIV testing; HIV = human immunodeficiency virus; ART = antiretroviral treatment.

MANAGEMENT OF TB AND ART IN HIV-POSITIVE TB PATIENTS

Circuit of TB patients in Thyolo

The circuit of TB patients in terms of TB management and ART in Thyolo District Hospital, Malawi, is shown in Figure 2.

Management of TB

All patients diagnosed with TB are registered and started on standardised anti-tuberculosis treatment according to national guidelines.[8] Table 1 shows the different TB treatment regimens and their indications. In the RMP-based initial phase of treatment, patients are admitted to the hospital TB wards for 2 weeks, during which they receive directly observed anti-tuberculosis treatment. During these 2 weeks they also receive information, education and communication (IEC) sessions on TB and HIV/acquired immunedeficiency syndrome (AIDS). They are then allowed to go home if fit enough, and receive the remaining 6 weeks of intermittent initial phase treatment under supervision of a health centre, a guardian (guardian-based treatment) or the hospital if the patient lives close by and agrees to continue treatment on an ambulatory basis. Drugs are administered three times a week, on Monday, Wednesday and Friday, over the 6-week period. Once patients have completed the initial

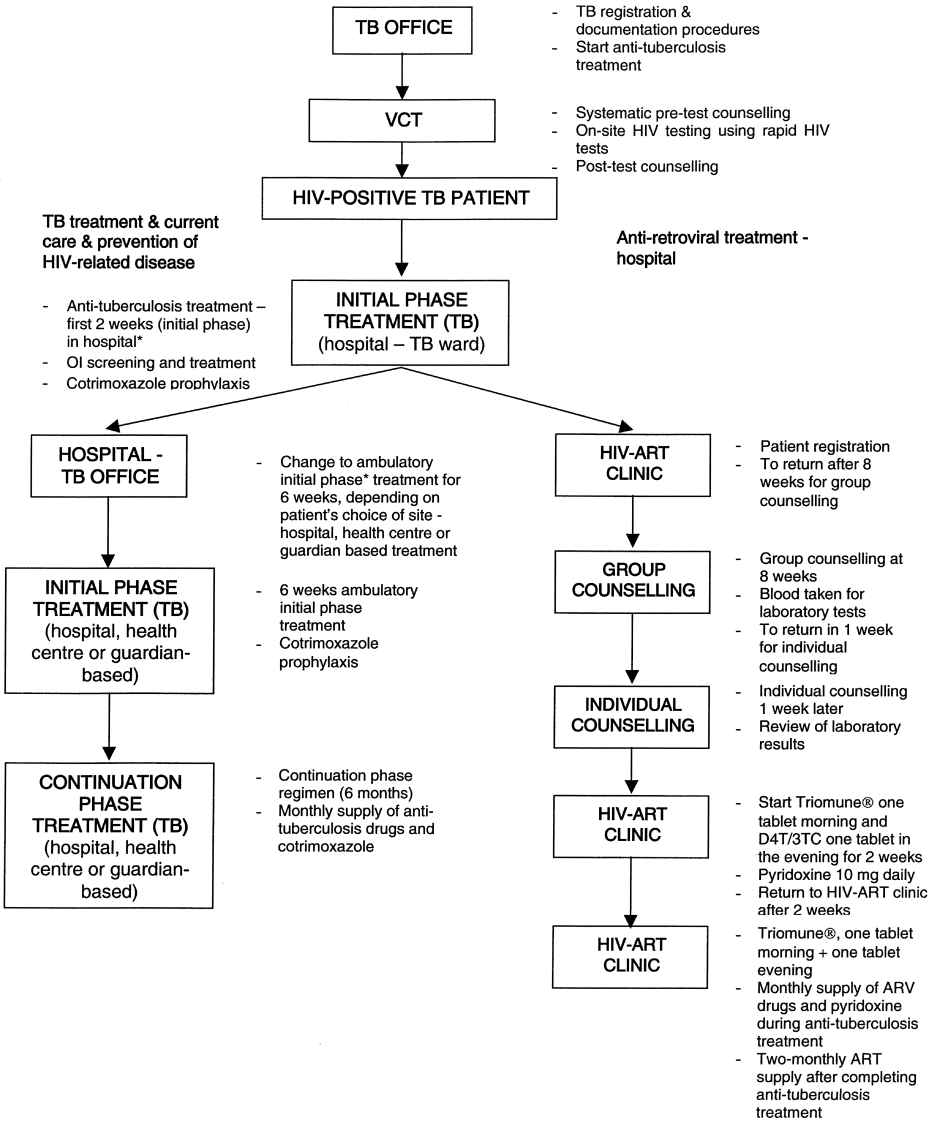

Figure 2 Circuit of a TB patient for receiving TB management and ART in Thyolo District Hospital, Malawi. *Supervised drug administration 3 times a week. VCT = voluntary counselling and HIV testing; OI = opportunistic infections; ART = antiretroviral treatment; D4T = stavudine, 3TC = lamuvudine, NVP = niverapine; Triomune® = fixed-dose combination of d4T/3TC/NVP.

phase, they are put on the 6-month continuation phase (HE), when they are given drugs on a monthly basis. All drugs and investigations for TB are free of charge.

VCT and HIV care-related activities

Since early 1999, all registered TB patients have been systematically offered access to HIV voluntary counselling and testing (VCT). Individuals undergo pre-test counselling on a one-to-one basis. HIV testing is done on site using rapid whole blood testing kits. Those who accept HIV testing are offered post-test counselling. HIV-positive individuals are offered co-trimoxazole (CTX) prophylaxis provided there are no contraindications.[9] CTX is taken during the entire course of anti-tuberculosis treatment, and indefinitely thereafter. The uptake of VCT and CTX in this setting has been over 90%,[9] and adherence to CTX during and after anti-tuberculosis treatment has been excellent.[10,11] All HIV-positive TB patients are also screened and treated for HIV-related opportunistic infections while on the ward, and all TB patients receive nutritional support while hospitalised. There are links with community care groups and home-based care volunteers who provide continuing support and enhance adherence through counselling.

ART regimens

The first-line ART regimen in Malawi consists of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP), available as a fixed-dose combination (FDC). The basic reasons for choosing this combination as a first-line regimen included the need for standardised therapy across the country, ease of administration (one

pill twice daily), few short-term side effects, no need for mandatory laboratory monitoring,[3,6] positive previous experiences and relatively low cost. Two three-drug FDCs of d4T, 3TC and NVP are currently available: d4T40/3TC/NVP (Triomune® or Triviro LNS®-40) for patients weighing ⩾60 kg and d4T30/3TC/NVP (Triomune® or Triviro LNS®-30) for those weighing <60 kg. A two-drug FDC of d4T and 3TC is also currently available: d4T40/3TC (Coviro LS®-40) and d4T30/TC (Coviro LS®-30) for individuals weighing ⩾ or <60 kg, respectively.

Zidovudine (AZT) can be used as an alternative to d4T in case of severe d4T-associated peripheral neuropathy. Efavirenz (EFV) replaces NVP in case of NVP-associated hepatitis, liver disease, severe skin reactions or if a patient is taking RMP-containing anti-tuberculosis treatment. The second-line regimen in case of failure of the first-line regimen is a combination of AZT, didanosine (ddI) and nelfinavir (NFV). This may be reviewed in the light of the recently released 2003 version of the WHO ART guidelines.[12]

ART eligibility for HIV-positive TB patients

In Malawi, individuals with TB are potentially eligible for ART because they are categorised as WHO Clinical Stage III or IV.[3,6] ART is not given during the initial phase of anti-tuberculosis treatment because of the interaction between RMP and NVP (all drug combinations in the initial phase of anti-tuberculosis treatment include RMP) (Table 1). Once the patient has completed the initial phase of treatment and has started on the continuation phase, consisting of INH and EMB, the patient is eligible to start ART. Because RMP has a long half-life, ART with D4T/3TC/NVP is only started after the patient has been on EH for 1–2 weeks.

Steps for providing ART for HIV-positive TB patients (Figure 2)

- HIV-positive TB patients are seen in the hospital HIV-ART clinic 8 weeks after starting anti-tuberculosis treatment in conjunction with a patient guardian. Due attention is paid to confidentiality and informed consent.
- The individual undergoes medical screening by the clinical officer and participates with the guardian in a group counselling session about antiretroviral (ARV) drugs, the importance of strict adherence to therapy and what to do in case of side effects.
- In Thyolo, blood is then taken for CD4-lymphocyte count, total lymphocyte count, haemoglobin and liver function testing (alanine aminotransferase, ALT) to monitor the current clinical admission and monitoring protocol. According to the current Malawi ART protocol, however, these tests are not mandatory.[6]
- One week later, when the laboratory results are available, the patient undergoes individual counselling on a one-to-one basis.
- The patient is weighed and prescribed Triomune®-30 or Triomune®-40, depending on body weight. In case of specific contraindications to NVP or D4T, respectively EFV or AZT could be considered as alternatives.
- Patients are given one tablet of Triomune® in the morning and one tablet of combined d4T/3TC (Coviro LS®) at night for 14 days. Treatment is introduced in this manner, with a lead in the NVP dose, due to the need to reduce the risk of NVP-induced rash.
- TB patients also receive EH, and pyridoxine 10 mg daily. If TB patients are taking CTX prophylaxis, this is also continued along with ART.
- Patients are reviewed at the HIV-ART clinic after the initial 2 weeks of ARV drugs.
- From then on, provided there are no side effects, patients are seen and given their drugs every 14 days, then every 28 days (4 weeks) until the end of anti-tuberculosis treatment. Once anti-tuberculosis treatment has been completed patients receive their drugs every 56 days (8 weeks). They are now advised to take one tablet of Triomune® in the morning and one in the evening. Thus, getting a patient onto a simple daily regimen of one pill of Triomune twice daily requires three visits to the hospital over a period of 3 weeks (Figure 2).
- If any side effects are experienced between clinic visits, patients are educated about the need to report to a health facility.
- Patients on the retreatment regimen containing RMP throughout are immediately considered for the alternative first-line ART regimen; e.g., d4T/3TC/EVF. Women placed on EFV are given appropriate contraceptive advice.
- ART and laboratory tests are provided free of charge in Thyolo.

OPTIONS FOR INCREASING THE UPTAKE OF ART IN HIV-POSITIVE TB PATIENTS

The possible options for trying to increase the current uptake of ART in HIV-positive individuals with active TB are not exclusive of one another and take into account the current first-line ART regimen as well as the patient circuit in Thyolo.

Option: Hospitalise HIV-positive TB patients for an initial period of 12 weeks

Rationale and advantages

In the current setting, TB treatment is centralised for an initial period of 2 weeks, after which it is decentralised. The ART programme, however, remains centralised at the hospital. HIV-positive TB patients starting ART will be expected to return to hospital several times, first for ART initiation and then for follow-up. In our setting, 25% of all newly registered TB patients are moribund on admission;[9] 57% are malnourished,

and 35% have moderate to severe malnutrition.[13] The majority of patients are destitute due to their chronic illness and the loss of work capacity. Expecting ill and destitute TB patients to travel to one site to receive their anti-tuberculosis treatment and then again to travel on multiple occasions to hospital for ART is likely to be unrealistic and unfeasible for most patients, particularly those living in remote areas.[14] Offering the option of remaining in hospital during the first 12 weeks of anti-tuberculosis treatment, when most ART-related visits are required, could introduce a number of potential advantages for the patient.

First, patients who are particularly ill or unable to make multiple journeys for any reason will be able to complete their initial phase of anti-tuberculosis treatment and initiate ART while in hospital. This would reduce the overall burden of travel. Second, the first 2 weeks of ART would be initiated on the ward, allowing the patient to be monitored closely. The longer period of hospitalisation is likely to have the additional advantage that HIV-related opportunistic infections are well taken care of and the nutritional status of most patients improves. Requesting patients to return to hospital once a month thereafter is less demanding and likely to be more feasible. Third, patients would have the added advantage of having access to hospital-based counsellors to clarify any additional concerns following the initial counselling sessions.

Operational considerations

The introduction of such a strategy has the following implications:

First, there will be a need to assess who might be willing to stay in hospital for 3 months from the start. This assessment could be undertaken during the initial counselling process.

Second, Malawi has progressively achieved decentralisation of anti-tuberculosis treatment.[7] This strategy has resulted in an improved turnover of patients in the TB wards, a large reduction in overall bed occupancy rates, and has probably brought economic savings to the health system.[15] Hospitalising HIV-positive TB patients, who comprise close to 77% of all newly registered TB patients[5] in our setting, would unavoidably reverse some of these gains, and TB wards run the risk of becoming over-congested again. In Malawi, total available bed space for all types of TB is generally limited, and individuals with smear-negative PTB or EPTB are often admitted to the general wards along with admissions for other medical conditions. As the HIV prevalence rate in smear-negative PTB and EPTB patients is close to 80%,[5] the option of hospitalising such patients for 3 months would undoubtedly reduce overall bed availability for patients with conditions other than TB. Furthermore, although patients with smear-negative PTB and EPTB are less infectious than those with smear-positive TB, there is still a risk of TB transmission.[16] In our setting, 50% or more of all non-TB patients admitted to medical wards are HIV-positive.[17] There is therefore a potential risk of nosocomial TB transmission to this group of susceptible individuals, if they spend longer periods of time with larger numbers of TB patients in already overcrowded conditions.

Third, for a patient to spend 3 months in a hospital, often far from home, is likely to have implications for the household in terms of transport logistics and time spent off work by family members visiting hospital. Patients with TB also tend to feel better after 2 weeks of anti-tuberculosis treatment and, in such circumstances, prefer to continue treatment in the community.[7] In Thyolo, which has a network of home-based care volunteers, peer groups and nurses providing continuing support and care within the community, this is another reason why patients might be inclined to return to their homes.

Fourth, an estimated 50% of Ministry of Health (MoH) posts remain unfilled,[18] and the increase in daily workload due to more TB patients on the wards is an important concern.

It is therefore unlikely that Malawi's National TB Programme (NTP) will want to hospitalise TB patients for 12 weeks, having already embarked on a policy of decentralisation.

Option: Decentralise ART to health centres after hospital-based initiation of ART

Rationale and advantages

If HIV-positive TB patients have been started on ART in the hospital setting, the option of decentralising the continuation of ART to health centres along with the continuation phase of anti-tuberculosis treatment would have a number of advantages.

First, the need to visit a health centre to collect the monthly supply of anti-tuberculosis drugs and then the hospital for the ART drugs could be avoided. The patient could collect the drugs for both the continuation phase of anti-tuberculosis treatment as well as ART at the health centre.

Second, the workload on a centralised hospital-based ART clinic would be progressively reduced as patient follow-up becomes decentralised to health centre level. This is an important consideration for scaling up ART. Some trained medical assistants and nurses working at health centres in Thyolo are already satisfactorily managing HIV-related opportunistic infections. Follow-up of patients who are stable and simply require regular supplies of ART should also be feasible in such centres.

Third, overall adherence to ART in the long term is likely to be enhanced, as individuals will have access to both TB and ARV treatment at a site closer to their residence. We have very encouraging evidence of adherence to CTX prophylaxis during and after anti-tuberculosis treatment in Thyolo.[10,11] Unlike the

current situation with ART, CTX prophylaxis is decentralised with anti-tuberculosis treatment, and is made available in all health centres. Patients thus receive their monthly supply of CTX along with their anti-tuberculosis drugs. We also know that patients are committed to taking their drugs and that those who stop treatment do so mainly because of transport problems associated with long distance travel.[11]

Operational considerations

Decentralising ARV drugs along with anti-tuberculosis drugs has a number of implications.

First, a mechanism is necessary to ensure regular ARV drug supply, monitoring and drug security to run in parallel with the existing system for anti-tuberculosis drugs.

Second, health centres need the capacity to dispense and monitor adherence to ARV drugs. Clinicians must also be able to recognise drug side effects, the immune reconstitution syndrome and treatment failure.

Third, adequate human resources are necessary to perform these additional tasks. Currently only 50% of available posts in the Malawi MoH are filled,[18] and 90% of health facilities are unable to deliver the essential health package.[19] ART cannot be decentralised without providing the necessary staff to fill existing gaps and to cover the additional needs for ART. Conditions of service are poor, and staff retention and motivation are important determining factors that will also need to be addressed.

Fourth, the decentralisation of ART will have to be extended to eventually cover all health centres in Thyolo district.

Option: Replace NVP in the current ART regimen with EFV

Rationale and advantages

When the two drugs are administered concomitantly, RMP reduces the blood levels of NVP. Increasing the dose of NVP to compensate for this interaction increases the risk of toxicity, and is thus not recommended.[12] ART with Malawi's current first-line regimen is thus deferred until after the completion of the initial phase of anti-tuberculosis treatment. As RMP has a long half-life, ART is started only 1–2 weeks after the last dose of RMP. Changing from NVP to EFV in the first-line ART regimen for HIV-positive TB patients would have the following advantages:

First, ART could be started during rather than 10 weeks after the initiation of anti-tuberculosis treatment. A regimen containing d4T, 3TC and EFV could potentially be started as early as 2 weeks after starting anti-tuberculosis treatment. Such a strategy would be in line with recent WHO recommendations.[12] The patient could then be hospitalised for a much shorter time. For example, after 2 weeks of initial phase anti-tuberculosis treatment, the patient could be started on ART and be discharged, to report back to hospital after 2 weeks for an assessment. Patients would thereafter return once a month to collect their monthly supply of drugs, or, if it becomes a reality, receive their anti-tuberculosis drugs as well as ART at the health centre level. In any case, such a strategy would provide the opportunity to adapt the duration of hospitalisation according to the clinical status and evolution of the patient.

Second, with EFV there would be no need for a lead-in dose during the first 2 weeks (unlike NVP). This would make ART initiation more straightforward for both health personnel and patients.

Third, we have demonstrated that early mortality in TB patients is a major operational problem in Thyolo[13] and countrywide in Malawi,[20] and that deaths in the first 2 months of starting anti-tuberculosis treatment can constitute up to 50% of overall TB mortality.[20] Introducing ART at an earlier stage may result in a reduction in the current case fatality rate, which is adversely affecting the credibility of the NTP in the eyes of health workers, TB patients and the community. By reducing case fatality rates, ART may also contribute to improving overall TB treatment outcomes.

Fourth, there is pressure in Malawi, as elsewhere in sub-Saharan Africa, to replace EH by RH during the continuation phase of anti-tuberculosis treatment to reduce rates of recurrent TB.[21] RH is also known to be a more efficacious combination than EH and is likely to benefit both HIV-positive and HIV-negative TB patients. As the price of RMP has decreased considerably in the last few years, cost issues are no longer an impediment to changing to RH.[22] Replacing NVP by EFV in the first-line ART regimen for HIV-positive TB patients would allow an eventual change from EH to RH in the continuation phase of anti-tuberculosis treatment without adversely affecting the feasibility of ART for HIV-positive TB patients. An ART regimen containing EFV would also allow standardisation of ART in all anti-tuberculosis regimens, which is currently not the case with ART for TB meningitis and recurrent TB (Table 1). A possible scheme for combined anti-tuberculosis treatment and an EFV-based ART regimen for HIV-positive TB patients in Thyolo is shown in Table 2.

Operational considerations

Replacing NVP by EFV would have a number of operational implications:

First, unlike the combination of d4T/3TC/NVP, the combination of d4T, 3TC and EFV is not yet available as an FDC. The immediate solution would be to use combined d4T and 3TC, which exists as an FDC, and give EFV separately. However, this pill burden will be unavoidably higher, making drug administration more difficult, and in turn possibly adversely influencing patient adherence. Furthermore, EFV is much more expensive than NVP and the overall cost of such a regimen would be higher. Advocacy for

Table 2 Possible scheme for combined anti-tuberculosis treatment and efavirenz-based ART treatment for HIV-positive TB patients in Thyolo

Timing*	Hospitalisation	TB treatment	Sputum smear†	IEC and access to VCT	ART treatment	ART consultation	ART counselling and drug supply
Day 1	Start of hospitalisation	Start of initial phase (2 months)	X				
Day 2–7				X		Medical screening	Group counselling
Week 2	End of hospitalisation				Start ART	X	Individual counselling
Week 4		Ambulatory continuation of initial phase				X	Individual counselling and ambulatory continuation of ART
Week 8		Start of continuation phase (6 months)	X			X	X
Week 12		X				X	X
Week 16		X					X
Week 20		X	X				X
Week 24		X				X	X
Week 28		X	X				X
Week 32		End of TB treatment				X	X
Week 40					Continue ART		X

* Scheduled visits occur at the end of the specific week.
† For smear-positive TB cases.
ART = antiretroviral treatment; HIV = human immunodeficiency virus; TB = tuberculosis; IEC = information, education, communication; VCT = voluntary counselling and HIV testing; X = scheduled visits.

making an EFV-containing FDC available at lower cost is urgently required. An intermediary option could be to substitute NVP for EFV after the completion of RMP-based TB treatment. This would allow available FDC combinations, which include NVP, to be used after anti-tuberculosis treatment. As both NVP and EFV belong to the same family of non-nucleoside reverse transcriptase inhibitors and are used in first-line regimens, such a strategy should not create the additional risk of resistance development or compromise the choice of second-line regimens.

Second, as RMP reduces the therapeutic drug levels of EFV, it is recommended that, in individuals receiving RMP as well as EFV, the dose of EFV be raised from 600 mg to 800 mg daily.[3] An eventual FDC combination for HIV-positive TB patients will have to take this into consideration. The effect of a 30% increase in standard daily dose of EFV on side effects in often weak, ill HIV-positive TB patients, who receive multiple anti-tuberculosis drugs at the same time, will also have to be evaluated closely.

Third, as EFV is known to be teratogenic, women of childbearing age would need to be offered effective, long-term contraception. Most TB patients in our setting believe that they cannot have sex during anti-tuberculosis treatment and actually abstain.[23] Although this is likely to reduce the overall risk of pregnancy during anti-tuberculosis treatment, all female TB patients would need to be offered contraception. For those women who wish to become pregnant, the possibility of changing from EFV to NVP at the end of anti-tuberculosis treatment would have to be considered. This aspect of care would have to be integrated into the counselling process, and TB programmes would have to ensure good links with family planning services. Effective contraceptive methods would have to be made available at the ART-TB clinics and staff trained in their use. Long-acting contraceptive preparations such as depo-provera would be ideal in these circumstances. Although this preparation is known to provide a higher blood hormone level than oral contraception, little is known about how EFV would affect its overall contraceptive efficacy.[12] In the absence of such evidence, it would be wise to recommend additional barrier contraception. Making male and female condoms available would also have the additional advantage of ensuring the prevention of secondary HIV transmission to partners.

Fourth, EFZ cannot be used in children aged ⩽3 years. Although not of major concern, of a total of 23 000 annually registered TB cases in Malawi in 1998, up to 1000 patients were aged ⩽3 years.[24]

Option: Integrate TB and ARV care into one clinic at hospital level

Rationale and advantages

TB and ARV treatment currently follow separate circuits at the hospital level (Figure 2). TB treatment is administered at the TB office and ART in a separate HIV-ART clinic. For HIV-positive TB patients, it should be possible to integrate TB treatment and ART into one clinic (the HIV-ART clinic). This is likely to have a number of advantages. The services would be more patient-friendly, as both services would be offered at the same site, thus avoiding multiple visits by patients

to different sites. This more 'holistic' approach may influence the patients' perception of the link between the two diseases, which in turn may positively influence ART-seeking behaviour in TB patients. If ART were decentralised to the health centre level, it is likely that both anti-tuberculosis treatment and ART would be managed by one clinician. It thus seems logical to try to ensure a similar approach at the hospital level.

Operational considerations

Such a move would imply good collaboration between the TB office and the HIV-ART clinic. Patient cards and anti-tuberculosis drugs for HIV-positive TB patients would need to be transferred at the end of the hospitalisation period to the HIV-ART clinic, and treatment for both conditions would have to be administered by the same clinician. Monitoring and cohort reporting of outcomes for each quarter, which is currently the responsibility of the district TB officer, would have to be done in close collaboration with the HIV-ART clinic staff. With the current high HIV prevalence rates in TB patients, it is possible that a substantial proportion of TB patients would accept ART and be managed at the HIV-ART clinic. Hospital management teams might consider moving one of their TB officers to the ART clinic on a full-time basis to assist with drug dispensing, monitoring, recording and reporting.

CONCLUSION

The WHO has set a target of putting over 3 million people on ART by 2005. It is likely that a substantial proportion of these will be HIV-positive individuals with TB who pass through the health system. Less than 5% of all individuals who require ART in sub-Saharan Africa currently have access to these drugs, and few programmes at district level offer ART to HIV-positive individuals with active TB. In Thyolo District Hospital, despite efforts to initiate ART for HIV-positive TB patients, we have ended up with a relatively low uptake. A hospital-based ART programme may simply not be accessible for a great proportion of patients who are also receiving anti-tuberculosis treatment.

In Thyolo, there are therefore unrecognised tensions between decentralised TB treatment and the current centralised ART delivery. Resolving this tension in different settings will need careful consideration before the correct operational strategy can be decided. The option of hospitalising TB patients for 12 weeks with d4T/3TC/NVP would be a retrograde step for NTPs that have worked hard towards decentralisation over the past 5–7 years. Replacing NVP by EFV in the first-line ART regimen, with the option of starting patients after the first 2 weeks of initial phase anti-tuberculosis treatment, seems a good option, as this would limit the period of initial hospitalisation for HIV-positive TB patients. The availability of an FDC that includes EFV would thus be vital to reduce the overall pill burden. Replacing NVP by EFV would also seem a rational step to allow standardisation of the first-line ART regimen across all current anti-tuberculosis regimens. In Thyolo, where the majority of TB patients are malnourished[13] and early TB mortality is extremely high,[20] an initial period of hospitalisation in those who require it should be considered, as it would seem a logical step to ensure appropriate management of opportunistic infections, nutritional rehabilitation and the careful introduction of ART. The combination of an initial period of hospitalisation for very ill TB patients along with early initiation of ART may positively influence the overall survival of HIV-positive TB patients in our setting.

Limiting ART delivery to hospitals will challenge WHO targets for 2005, and there is an urgent need to find solutions that will enable districts such as Thyolo to decentralise ART along with TB treatment. The need to decentralise ART also applies to all HIV-positive individuals. The challenges of decentralisation to dilapidated health centres with limited staff, who are generally poorly qualified and demotivated, will have to be addressed. The way forward is one in which TB and HIV programmes will need to entertain the philosophy of 'learning by doing'.

We have been late in the 'doing', and many thousands of HIV-infected patients in Malawi, as in other countries in sub-Saharan Africa, have died of AIDS due to the lack of ART. We must now rapidly face the uphill task of trying to get more people on ART. The debate around 'ways forward' in getting more HIV-positive TB patients who pass through the health system on ART is part of the struggle.

ART cannot be given in isolation, and it needs to be placed within a suitable framework of service delivery.[25] Making existing decentralised services suitable for ART delivery means that they will have to be adapted and improved quickly. The availability of financial and human resources will be a crucial prerequisite for overcoming the deficiencies that are currently a serious obstacle to rapid ART decentralisation. These resources must be made available. Otherwise, for HIV-positive people who need ART in districts such as Thyolo, the WHO targets for 2005 will remain a myth, and many HIV-positive TB patients will continue to die.

Acknowledgements

The views expressed in this article are those of the authors alone and do not necessarily reflect the stated policy of the WHO. We are grateful to the Thyolo district hospital management and particularly the Malawi NTP for the excellent collaboration and encouragement in trying to implement joint TB-HIV activities, including ART in Thyolo. We are also grateful to the National AIDS Commission for their continued support. The joint TB-HIV support programme including ART is supported by Médecins sans Frontières. We are grateful to the UK Department for International Development (DFID), the Norwegian Agency for Technical Cooperation (NORAD), the Royal Netherlands TB Association (KNCV), USAID and STOP-TB, WHO, for supporting TB and TB-HIV control countrywide in Malawi.

References

1 Raviglione M C, Harries A D, Msiska R, et al. Tuberculosis and HIV. Current status in Africa. AIDS 1997, 11: 115–123.
2 Harries A D. Issues facing TB control. Tuberculosis control in sub-Saharan Africa in the face of HIV and AIDS. Scott Med J 2000; 45: 47–50.
3 World Health Organization. Scaling up anti-retroviral therapy in resource-limited settings. Guidelines for a public health approach. WHO, QV268.5. Geneva, Switzerland: WHO, 2002.
4 National AIDS Commission of Malawi. National estimate of HIV/AIDS in Malawi in 2003. Lilongwe, Malawi: National AIDS Commission, 2004.
5 Kwanjana J H, Harries A D, Gausi F, Nyangulu D S, Salaniponi F M L. TB-HIV seroprevalence in patients with tuberculosis in Malawi. Malawi Med J 2001; 13: 7–10.
6 Ministry of Health and Population and National AIDS Commission. Guidelines for the use of anti-retroviral therapy in Malawi. 1st ed. Lilongwe, Malawi: Ministry of Health and Population, 2003.
7 Salaniponi F M, Gausi F, Mphasa N, Nyirenda T E, Kwanjana J H, Harries A D. Decentralisation of treatment for patients with tuberculosis in Malawi: moving from research to policy and practice. Int J Tuberc Lung Dis 2003; 7 (Suppl 1): S38–S47.
8 Manual of the National Tuberculosis Control Programme in Malawi. 5th ed. Lilongwe, Malawi: Ministry of Health and Population, 2002.
9 Zachariah R, Spielmann M P, Chingi C, et al. Voluntary counseling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi. AIDS 2003, 17: 1053–1061.
10 Zachariah R, Harries A D, Arendt V, et al. Compliance with cotrimoxazole prophylaxis for the prevention of opportunistic infections in HIV-positive tuberculosis patients in Thyolo district, Malawi. Int J Tuberc Lung Dis 2001; 5: 843–846.
11 Zachariah R, Spielmann M P, Harries A D, Gomani P, Bakali E. Cotrimoxazole prophylaxis in HIV-infected individuals after completing anti-tuberculosis treatment in Thyolo, Malawi. Int J Tuberc Lung Dis 2002; 6: 1046–1050.
12 World Health Organization. Scaling up anti-retroviral therapy in resource-limited settings: treatment guidelines for a public health approach. WHO, QV268.5. Revised version. Geneva, Switzerland: WHO, 2003.
13 Zachariah R, Spielmann M P, Harries A D, Salaniponi F M L. Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early deaths. Trans Soc Trop Med Hyg 2002, 96: 291–294.
14 Kapulula P K, Chilimampunga C, Salaniponi F M L, Squire S B, Kemp J. The journey towards TB diagnosis: preferences of the people of Mtsiliza, Lilongwe. Int J Tuberc Lung Dis 2001; 5 (Suppl 1): 167.
15 Floyd K, Skeva J, Nyirenda T, Gausi F, Salaniponi F. Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. Int J Tuberc Lung Dis 2003; 7 (Suppl 1): S29–S37.
16 Behr M A, Warren S A, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. Lancet 1999; 353: 444–449.
17 Lewis K, Callaghan M, Phiri K, et al. Prevalence and indicators of HIV and AIDS among adults admitted to medical and surgical wards in Blantyre, Malawi. Trans Roy Soc Trop Hyg 2003; 97: 91–96.
18 Ministry of Health and Population. Malawi National Health Plan 1999–2004. Volume 2: National Health Facilities Development Plan (1999). Lilongwe, Malawi: Ministry of Health and Population, 1999.
19 Ministry of Health and Population. Malawi Health Facility Survey report. Planning Unit. Lilongwe, Malawi: Ministry of Health and Population, 2003.
20 Harries A D, Hargreaves N J, Gausi F, Kwanjana J H, Salaniponi F M L. High early mortality in tuberculosis patients in Malawi. Int J Tuberc Lung Dis 2001; 5: 1000–1005.
21 Harries A D, Chimzizi R B, Nyirenda T E, Gorkom Van J, Salaniponi F M. Preventing recurrent tuberculosis in high HIV-prevalent areas in sub-Saharan Africa: what options for tuberculosis control programmes? Int J Tuberc Lung Dis 2003; 7: 616–622.
22 van Gorkom J, van Cleeff M, Becx-Bleumink M, Veen J. Short-course instead of long-course chemotherapy for smear-negative patients in sub-Saharan Africa. Int J Tuberc Lung Dis 2001; 5: 4–11.
23 Salaniponi F M L, Christensen J, Gausi F, Kwanjana J H, Whitty C J M, Harries A D. 'No sex please'—we're on TB treatment. Trans Roy Soc Trop Med Hyg 2000; 94: 39–40.
24 Harries A D, Hargreaves N J, Graham S M, et al. Childhood tuberculosis in Malawi: nationwide case-finding and treatment outcomes. Int J Tuberc Lung Dis 2002; 6: 424–431.
25 Jong-Wook L. Global health improvement and WHO: shaping the future. Lancet 2003; 362: 2083–2088.

RÉSUMÉ

L'OMS s'est fixé comme objectif de traiter 3 millions de personnes au moyen du traitement antirétroviral (ART) d'ici 2005. En Afrique subsaharienne, les patients tuberculeux (TB) séropositifs pour le VIH pourraient contribuer à cet objectif de manière significative. L'ART (stavudine/lamivudine/nevirapine) a été mis en route dans le district de Thyolo au Malawi en avril 2003, où tous les patients TB séropositifs ont été considérés comme éligibles et se sont vus offrir l'ART. Malgré ceci, 44 seulement des 352 patients TB (13%) ont été effectivement mis sous ART à la fin novembre 2003. Actuellement, la plupart des patients TB quittent l'hôpital après 2 semaines pour achever dans la collectivité la phase initiale de leur traitement antituberculeux (basé sur la rifampicine) et l'ART est offert aux patients TB séropositifs après qu'ils aient commencé la phase de continuation du traitement (isoniazide/éthambutol). L'ART n'est offert qu'à l'hôpital, alors que la majorité des patients TB prennent la phase de continuation de leur traitement antituberculeux dans les centres de santé. Pour cette raison, les patients TB séropositifs rencontrent des difficultés pour accéder à l'ART.

Dans cet article, nous discutons une série d'options de façon à augmenter la prise en charge de l'ART chez les patients TB séropositifs pour le VIH. Les options principales sont 1) l'hospitalisation des patients TB séropositifs avec en vue le démarrage à l'hôpital de l'ART dans la phase de continuation ; 2) la décentralisation de l'administration de l'ART de sorte que celui-ci puisse être administré dans les centres de santé ; 3) le remplacement de la nevirapine par l'efavirenz, ce qui permettrait de commencer l'ART plus tôt dans la phase initiale du traitement antituberculeux. La décentralisation de l'ART depuis les hôpitaux vers les centres de santé améliorerait considérablement son accessibilité.

RESUMEN

La OMS fijó como objetivo para 2005 tratar 3 millones de personas con tratamiento antirretrovírico (ART). En África subsahariana, los pacientes con tuberculosis (TB) y serología positiva para el VIH podrían representar una proporción considerable de este objetivo. El ART (estavudina, lamivudina y nevirapina) se aplicó por primera vez en abril de 2003 en el distrito de Thyolo en Malawi ; se consideró que todos los pacientes seropositivos con TB eran idóneos y se les propuso el ART. Sin embargo, a fines de noviembre de 2003 sólo 44 (13%) de los 352 pacientes con TB habían comenzado el ART. En la actualidad, la mayoría de los pacientes con TB vuelven a la comunidad después de 2 semanas de hospitalización y deben completar a domicilio la fase inicial del tratamiento anti-tuberculosis (con rifampicina) ; además, el ART se ofrece a los pacientes seropositivos con TB después del comienzo de la fase de continuación del tratamiento anti-tuberculosis (isoniacida y etambutol) y exclusivamente en medio hospitalario. Dado que durante la fase de continuación la mayoría de los pacientes recibe el tratamiento anti-tuberculosis en los centros de salud, el acceso al ART es difícil para los pacientes seropositivos con TB.

En este artículo se discuten una serie de opciones para incrementar la administración del ART a los pacientes seropositivos con TB. Las principales opciones son : 1) hospitalizar los pacientes con TB y seropositivos con el propósito de comenzar el ART, durante la fase de continuación en medio hospitalario ; 2) descentralizar el suministro del ART, para poder administrarlo en los centros de salud ; 3) reemplazar la nevirapina por efavirenz, de manera que el ART pueda comenzarse más temprano, en la fase inicial del tratamiento anti-tuberculosis. La descentralización del ART de los hospitales hacia los centros de salud mejoraría significativamente la accesibilidad del ART.