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HATiP

HIV & AIDS Treatment in Practice

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In this issue:

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NAM, 77a Tradescant Road, London, SW8 1XJ, UK

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HIV and TB in Practice for nurses: Starting ART for treatment and prevention in people with active TB and HIV

By Theo Smart

This edition of HATIP is part of a series targeted to nurses and other healthcare workers involved in providing care to people living with HIV in sub-Saharan Africa, kindly supported by the HIV/AIDS Department of the World Health Organization (WHO), Switzerland.

Thanks to Dr Eyerus Negussie and colleagues in the HIV/AIDS Department, Dr Haileyesus Getahun (STOP TB Department, WHO) and to Dr Reuben Granich (UNAIDS) for comments on this edition.

These special editions of HATIP are intended to support the capacity development of nurses and other healthcare staff as they take on new roles and tasks in the scale-up of HIV counselling and testing, antiretroviral treatment, HIV/TB activities, TB case finding, diagnosis, treatment and cure.

One of our goals with these editions is to draw out key messages and issues addressed in HATIP, the HATIP blog, and www.aidsmap.com news coverage relevant to nurses and others providing counselling, medical care and support services; and then to link these to related job aids, training materials, posters and training manuals that may be useful.

Introduction

This issue focuses on important interventions to manage people with TB in settings where HIV is common — starting with provider-initiated HIV testing and counselling. When they are found to also be HIV positive, the World Health Organization recommends antiretroviral therapy (ART) to all people with active TB and that ART be started as soon as possible — while the patient is still in the intensive phase of TB treatment or in the first eight weeks of initiation of TB treatment. In fact, it could be a matter of life or death, especially in people with advanced HIV disease.

Combined treatment of TB and HIV greatly reduces the risk of the person in your care dying. Antiretroviral therapy also prevents the progression of HIV disease, reduces the chances of another opportunistic infection that could make management of care more complicated, and reduces the chances of TB recurring.

At the same time, treating both conditions at once could be challenging because of side-effects, pill burden, and drug-drug interactions. Furthermore, nurses should be aware that some patients (especially the sicker ones) may have a complication, after starting ART, that makes it look like the TB is getting worse. This complication is called immune reconstitution inflammatory syndrome (IRIS). Obviously, the nurse will want to be able to tell this apart from TB that is getting worse (drug-resistant TB).

The nurse should also know that most cases of TB IRIS are transient or easily manageable, but there may be occasional cases that will need to be referred or where the nurse will have to consult a mentor or specialist.

What physical signs should nurses learn to look for? What should they do when IRIS occurs? When should they consult a specialist and when should they refer?

As long as the nurse recognises what they can manage, and what they may need support for, and when to refer urgently, he or she will do fine. Follow your national guideline.

Did you know?

Did you know that in sub-Saharan Africa most people with TB:

- **also have HIV**
- **frequently find out they have HIV only after getting TB**
- **if they have advanced HIV, may have a better chance of survival if they start antiretroviral treatment (ART) as soon as possible after going on TB treatment**
- **People who have TB and HIV have two life-threatening conditions that both need to be diagnosed and treated as soon as possible.**

Many people may be unaware they have HIV for years because they feel and look absolutely fine.

Then they suddenly get sick, sometimes very sick.

Maybe it starts with a cough, a fever, or night sweats. They begin to lose weight and they may notice that their lymph nodes are swollen.

Some people may go to a health facility while others will delay, or first go to their traditional healers — if they are lucky their sangoma has learned to recognise the symptoms of TB and will direct them to a facility that can diagnose TB.

What happens next depends upon how TB and HIV services are delivered in their country and the level of facility where the patient presents. In some countries, TB care is only delivered at TB clinics, which are sometimes part of a larger referral hospital, sometimes a stand-alone TB facility. In other countries, any clinician can treat TB, including nurses at the TB clinic or primary healthcare clinic (PHC). Regardless of the approach, studies show that people do best if they can get their HIV treatment from the same care provider while they are getting TB treatment.

Any clinic that treats people with TB who may also have HIV, should also be able to provide certain services that people with both infections require for as long as they are on TB treatment (as recommended by WHO's Policy on HIV-TB Collaborative Activities). These services are:

- HIV testing and counselling, including couples counselling
- HIV prevention services for the patient and their partners, and, if pregnant, effective referrals to Maternal Newborn and Child Health (MNCH) services
- Cotrimoxazole preventive therapy
- HIV prevention, treatment and care services (including regular screening for common opportunistic infections, followed by diagnosis and treatment) — with continuity of care at completion of TB treatment
- Antiretroviral treatment.

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If the TB facility or PHC cannot offer these services, start TB treatment and the patient will need to be referred for ART. However, this won't be as convenient for the patient, and referral could prolong the time before starting lifesaving treatment. There is also the risk that the patient won't be able to complete the referral and so become lost to follow-up. This is why an accompanied referral, supported by a community peer supporter, seems to be a very good way of making sure that people diagnosed with both TB and HIV make it to the ART site.

A TB patient's HIV status is a critical piece of information needed to manage their care appropriately. Any person who presents to the clinic with symptoms of TB should be offered HIV testing and counselling services unless they are already known to be HIV-positive. The patient could decline the test, but if they do, it should be offered again when they come back for the results of their TB tests. Testing should also be offered to the patient's partner and children where necessary. If a counselling and testing service that visits the family home is available, this may be a good way of encouraging other members of the family to learn their HIV status.

If the nurse who is presenting lab results and starting a TB patient on treatment does not see an HIV test result in the patient's file, or if the patient hasn't tested for HIV very recently, he or she should be offered HIV counselling and testing services immediately.

A recent publication from the International Union against Tuberculosis and Lung Disease, Implementing Collaborative TB-HIV Activities: A Programmatic Guide 2012, provides helpful advice for TB services which want to provide HIV testing and counselling services. It also provides case studies that describe the positive impact of very simple changes in service delivery, such as moving the location of an HIV testing service within the facility.

Case studies

Case studies source: Implementing Collaborative TB-HIV Activities: A Programmatic Guide 2012 (International Union against Tuberculosis and Lung Disease).

Case study 1: Improved uptake of HIV testing in a TB clinic when performed by TB nurses, Zimbabwe

In Zimbabwe, the programme to prevent mother-to-child HIV transmission was the first programme to offer HIV testing at the primary healthcare level. Therefore, the HIV testing room was frequently situated near the antenatal care rooms.

At the start of the Union-supported TB-HIV activities in Harare and Bulawayo, the HIV testing uptake ranged from 65 to 76%, and staff working in the TB rooms at the pilot sites wanted to find ways to make testing universal. They observed that male TB patients were hesitant about visiting the antenatal care wing and mixing with pregnant women, even if they wished to get tested. Consequently, the team decided that all TB patients should be tested by the TB nurses in the TB rooms. This simple change resulted in an increase in the HIV testing uptake to 95 to 100% of these patients.

Case study 2: HIV testing and counselling for family contacts of HIV-positive TB patients, Zimbabwe

The International Union against Tuberculosis and Lung Disease supported pilot clinics in Harare and Bulawayo, Zimbabwe, offer HIV testing and counselling to family and sexual contacts of HIV-positive TB patients. Clinic records show that in 2010, 677 index patients had 234 family contacts who wanted to be tested for HIV. Of these tested individuals, 175 (75%) were found to be HIV positive. Of this group, half were medically eligible for ART and cotrimoxazole preventive therapy (CPT) in their own right.

This example shows that by offering HIV testing and counselling to family members and sexual partners of HIV-positive TB patients, more individuals in need of ART and HIV care can be reached. In this way, increased coverage of life-saving services can be facilitated.

Either way, people may get their HIV and TB test results at approximately the same time. This may be a lot to handle all at once, so it is important to make sure that they receive the best available counselling and support.

If the patient is willing, he or she should be linked to an expert patient from their community — someone who has been in a similar situation — who can look out for them by making home visits, and accompanying them to clinic visits. This has been shown to increase the likelihood that they will be retained in care. A future issue will explore how to link patients with care and support, if your facility has few structured services available onsite.

When a patient has both TB and HIV, it is important to treat both conditions

A guide from the South African Department of Health gives just a few reasons why:

- HIV increases the rate of recurrence of TB (treatment of HIV reduces it)
- People with active TB who are co-infected with HIV have a higher risk of death compared to those who are HIV negative (16-35% in HIV-positive people vs 5-8% in HIV-negative people).
- Active TB increases the risk of HIV-associated mortality both during and after successful TB treatment.

If the person with TB and HIV is not already on ART, **TB treatment should be started first.** TB is the most common cause of death in people with HIV and treatment cannot be delayed. Furthermore, it is highly transmissible and treatment is needed to reduce the risk of TB being spread within the health facility, the community and the home.

Even so, the nurse should **start preparing the patient to take ART**. Soon after the patient has started and seems to be stable on TB treatment, **ART should be started, according to WHO, in *all* TB patients living with HIV no matter what their CD4 cell count is**. Not every country has endorsed this policy yet, though the country with the most coinfected patients — South Africa — has.

Countries where ART is already recommended for TB patients with HIV, irrespective of CD4 count

Algeria	India	South Africa (in cases of MDR-TB)
Bangladesh	Indonesia	Swaziland
Botswana	Italy	Tanzania
Brazil	Kenya	Ukraine
Burundi	Malawi	USA
Cambodia	Namibia	Venezuela
Chile	Nepal	Zimbabwe
Ecuador	Nigeria	
Haiti		

As well as reducing the risk of death in people with active TB, ART is important to prevention of TB. HIV treatment reduces the risk of developing active TB by almost two-thirds in people with higher CD4 counts (above 350), and by 84% in the people at highest risk, those with advanced HIV disease (CD4 counts below 200). Putting obstacles in the way, like requiring CD4 counts and then waiting for

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the results, doesn't make sense when ART does such a good job of reducing the risk of TB in all patients.

The urgency of HIV treatment in people with TB and low CD4 counts

In people with more advanced HIV disease and TB, clinical studies have shown that if ART doesn't start by the end of the intensive phase of TB treatment, survival and other outcomes are poorer. If HIV is very advanced — with CD4 cell counts below 50 — ART should be initiated as soon as possible within the first two weeks of starting TB treatment. Any delay could cost the patient's life.

But aside from the fact that it is urgent to treat people with TB who have low CD4 counts with ART as quickly as possible, there are differences of opinion among experts about when exactly is the best time to start ART in other patients. The policy in some countries is to wait even longer than the WHO recommendation to start within 8 weeks of starting TB treatment.

Some of the concerns relate to the fact that treating the two illnesses together is more complicated than treating someone for these two illnesses one after the other, due to drug-drug interactions and overlapping toxicities between HIV and TB drugs. It is important to know that these problems are manageable, and should not be an obstacle to starting treatment and saving a person's life.

The TB drug rifampicin substantially reduces the blood levels of many antiretroviral drugs, (nevirapine and most protease inhibitors). In order to avoid harmful declines in ARV drug levels, guidelines now recommend that TB therapy should be taken with an efavirenz-based ARV regimen, wherever possible.

Another concern is that TB and HIV drugs also have some overlapping toxicities. For this reason it is preferable to use tenofovir and 3TC or FTC as the backbone for HIV therapy wherever possible. Where this is not possible, the table below indicates the possible overlapping toxicities.

Toxicity	ARVs causing this toxicity	TB drugs causing this toxicity
Nausea and vomiting	Didanosine, zidovudine, protease inhibitors	Pyrazinamide, ethionamide, PAS
Hepatitis	Nevirapine, efavirenz, Protease inhibitors (especially when dose is increased to overcome rifampicin induction)	Rifampicin, isoniazid, pyrazinamide
Peripheral neuropathy	Stavudine, didanosine	Isoniazid, ethionamide, terizidone/cycloserine
Neuropsychiatric side-effects	Efavirenz	Isoniazid, terizidone/cycloserine, quinolones, ethionamide
Renal toxicity	Tenofovir	Aminoglycosides, capreomycin, rifampicin
Rash	Nevirapine, efavirenz	Rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin

Antiretroviral treatment in people with TB should only be halted for the same reason as in other people with HIV – if there is an immediate risk of a severe, life-threatening toxicity: severe rash or hypersensitivity reaction (nevirapine or abacavir) or severe hepatitis. In all other cases antiretroviral drugs should be changed according to local guidelines in order to determine whether antiretroviral treatment is causing or making worse the toxicity.

TB immune reconstitution inflammatory syndrome

The number one reason given for not starting ART in people with HIV and TB coinfection is the increased risk of TB immune reconstitution inflammatory syndrome (IRIS). Is this good reason to delay treatment, and how can the risk be managed? What should the nurse be aware of?

TB IRIS generally occurs within the first six months of starting ART (usually in the first few weeks) when the recovering immune system suddenly reacts in counterproductive ways to infections. This triggers worsening of existing TB symptoms, a recurrence of old symptoms in someone already taking appropriate TB treatment (paradoxical IRIS), and sometimes, new manifestations of the disease, like extrapulmonary TB (such as severe purulent TB infections in the lymph nodes). In other people, TB IRIS may 'unmask' a case of TB that hadn't been recognised (or shown any symptoms) or had been missed before initiation of ART.

Some of the symptoms of TB IRIS might not seem to be TB-related, like jaundice, neurological symptoms or nausea and vomiting. IRIS-like reactions to other opportunistic infections could be happening at the same time.

ART does not *cause* TB IRIS. The immune system does. It is trying to throw unwanted guests out of the body.

What is happening is more like this: picture the immune system as being like a great boxer or warrior who has been knocked out in the battle with HIV. While it has been unconscious, TB or other infections set up little colonies in different places in the body. When ART comes in to save the day, the immune system starts to recover — but is a bit dazed and confused for a while. It may look around and see signs of one of these TB colonies. Then it flies into a rage and responds with too much force. The more extensive the infection, the more problems it can cause — and the most widespread infections are likely to be in the people who had the most compromised immune systems when they started ART — and in whom TB treatment hasn't had the chance to clear up, especially early in the course of TB treatment.

How common is it? Common enough that any nurse treating TB patients with advanced HIV disease will probably see it. The reported frequency varies depending on how low the CD4 counts were in the cohort when ART is started. In some recent studies in people with advanced HIV infection, IRIS was found in somewhere between one in ten and one in four of patients who responded to effective ART, while other studies looked at how common IRIS was in people who already had opportunistic infections when they started ART, and reported rates of between one in seven and one in five. Usually IRIS was reported to be mild and resolved on its own. But some of these conditions caused patients tremendous suffering and, in other cases, IRIS was quite aggressive and life threatening, and some patients died.

Avoiding IRIS certainly sounds like a good idea but, in advanced patients, the option of delaying ART even for a few weeks does not exist in the vast majority of cases.

Three major studies suggested the best time to start antiretroviral treatment in people taking TB treatment depends upon the patient's CD4 cell count. Taken together, these studies show that:

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- People with TB and a very low CD4 count (below 50) require ART **urgently**, and need to start within two weeks of starting TB treatment
- All other patients with HIV and TB need to start ART within eight weeks of starting TB treatment.

Caution is needed in cases of TB meningitis; immediate ART is associated with more severe adverse events in these cases.

The risk of IRIS was higher in people with more advanced HIV disease.

Study:	Setting:	Key enrolment criteria:	Median CD4 (IQR):	Primary endpoint:
CAMELIA (Blanc, ANRS)	Cambodia	Smear+, CD4 < 200	25 (10-56)	Death
STRIDE (Havlir, ACTG)	Multi-national	Clinical TB, CD4 < 250	77 (36-145)	AIDS or death
SAPIT (Abdool-Karim, CAPRISA)	South Africa	Smear+, CD4 < 500	150 (77-254)	AIDS or death

Sources: AIDS 2010 abstract THLBB106, CROI 2011 abstract 38, CROI 2011 abstract 39LB, NEJM October 22 2011.

The studies showed that starting ART sooner after starting TB treatment is associated with a higher risk of IRIS — but the people most at risk of IRIS are those most at risk of death without ART, and the risk-to-benefit ratio is strongly in favour of early ART.

Basing the decision of when to start ART in people with TB and clearly advanced HIV on a CD4 cell count result could delay and increase the risk of death. Requiring a CD4 cell count result to decide how soon to start treatment, and then waiting up to two weeks for the result, defeats the objective of using the CD4 count to fast-track patients. By the time the result comes back it may be too late.

IRIS shouldn't scare any qualified nurse away from starting ART in someone with HIV and TB — that action may save their life.

But nurses should be on the lookout for IRIS once a patient has started ART, and also look for TB before initiation of ART.

Before ART is started, it is important to remember the other collaborative activities WHO recommends for better care for people living with TB and HIV: they should be provided with a comprehensive package of prevention, diagnosis, treatment and care interventions for HIV. This includes clinical and immunological staging and diagnosis and treatment of any opportunistic infections.

"The people most at risk of dying, those with CD4 <50, probably have other undiagnosed, untreated OIs that will actually kill them – like cryptococcal meningitis," Stacie Stender, a nurse working with JHPIEGO told HATIP. Indeed, in a number of studies on IRIS, most of the fatalities showed signs of cryptococcal IRIS. Any time there appears to be central nervous system involvement with raised intracranial pressure, such as with cryptococcal and tubercular meningitis, the nurse should *not* start ART, but refer the patient to a physician. If this is only discovered *after* ART has been started and IRIS begins causing inflammation in the central nervous system, it will take a specialist to manage it aggressively with corticosteroids — and even then, the prognosis is not good.

In addition, a number of details observed in the initial assessment and when lab results are returned could help flag a higher risk of IRIS, allowing the nurse to develop a plan with expert patients or community-based organisations to keep a closer eye on these patients.

Risk factors for IRIS at baseline

- A CD4 cell count < 50
- A CD4 % <7
- Anaemia (haemoglobin <100 g/l)
- World Health Organization (WHO) clinical stage 3 or 4
- A body mass index (BMI) of less than 18.5kg/m(2)
- High viral load

Risk factors for IRIS after starting ART

- A CD4 lymphocyte count increase >0.5/µL/day (a very good response to ART)
- Very good adherence (this is likely to encourage a good CD4 response)
- Night sweats during ART initiation
- Failure to show improvement in physical health on ART and TB treatment

"Adults and children on ART and TB treatment should feel better, with more energy and resolution of specific symptoms. If this isn't happening or there is a change from better to worse, there is a problem," Dr Doug Wilson, Chief of Infectious Diseases at Edendale Hospital, a large tertiary facility in Kwazulu Natal told HATIP.

Those are signs that the nurse should get support or call a specialist, but with increasing severity the patient will need to be referred up to the next level of care.

When to refer HIV-TB patients: deterioration symptoms checklist

- Nausea and vomiting – refer if severe; also check ALT in all with nausea and vomiting and refer if ALT > 100
- Severe abdominal pain
- Return of TB symptoms with HR > 120, RR > 30 or Temp > 39^{o}C.
- Loss of weight > 5kg
- Jaundice
- New skin rash or mouth ulceration
- Severe weakness, patient needs assistance to walk
- Patients with 'unmasking' TB IRIS may develop rapid onset of respiratory symptoms resembling bacterial pneumonia and sometimes respiratory failure, and should be referred *immediately*.
- Massive painful node enlargement
- Respiratory distress
- Airway compression or
- Neurological manifestations that require doctors' assessment

Dr Wilson suggested the following, as 'Alert symptoms' to detect cases that may be due to IRIS:

Acute symptoms (hours to days)	Chronic (weeks)
Prostration, shortness of breath, delirium, cough, chest pain, abdominal pain, vomiting, headache, hypotension, tachycardia.	Weight loss, fevers & chills, night sweats, small bowel diarrhoea and swelling of lymph nodes, and effusions.

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Other potential causes of failure to thrive must also be considered, especially multidrug-resistant TB (MDR-TB), but also non-adherence, malignancies and other opportunistic infections, and primary HIV drug resistance.

Check for these symptoms and, if you are partnering with expert patients and community health workers, advise them to be on the lookout. They should alert you so that you can intervene to support the patient to continue treatment and not drop out of care. When a case is detected, it can generally be managed, if it is either referred or the nurse has the support of a mentor or a doctor, without having to stop treatment — which would arguably pose a greater risk to the patient.

Summary checklist

When should you start ART in a person diagnosed with HIV and TB?

START TB TREATMENT FIRST
Make certain the patient is tolerating TB medications in the first 8 weeks of starting TB treatment.
Begin preparing for ART:

- Measure CD4 cell count (if available), prepare for adherence, check haemoglobin, creatinine (if indicated)
- Perform an initial clinical assessment, stage patient, look for any other opportunistic infections that need to be managed (serum cryptococcal antigen)
- Identify patients at greater risk of serious IRIS, e.g. any meningeal disease, consider referral of these patients now to a higher level of care. Look for signs of TB meningitis, and measure serum cryptococcal antigen if possible.
- Plan for closer follow-up of patients at higher risk of IRIS.

THEN,
following national protocols, start ART as soon as possible**:**

WHO *strongly* recommends starting ART in all TB patients living with HIV *irrespective* of their CD4 counts
and not later than 8 weeks after starting TB treatment.

Are there CD4 cell count results for the patient? If not, do not delay. People with TB and HIV are eligible for ART at any CD4 cell count.

Are the CD4 cell counts below 50?
In advanced AIDS (CD4 < 50) ART is URGENT: Start immediate ART within the first two weeks of TB — treatment improves survival
There is an increased risk of immune reconstitution inflammatory syndrome (IRIS, including fatal IRIS) — a temporary worsening, recurrence or new appearance of TB symptoms
The benefits of early treatment outweigh the risk of TB-IRIS for most patients.

- Close monitoring of those at greatest risk of TB-IRIS
- Immediately refer patients with unmasking TB IRIS
- Consult or refer other aggressive symptoms
- Manage milder cases of paradoxical IRIS

CD4 > 50:?
WHO say start ART as soon as possible, within the first eight weeks of TB treatment
But follow national guidelines

No CD4 cell count results for the patient?
Consider starting ART based upon clinical assessment of Stage 4 disease by week two, initiating all the other patients as soon as possible thereafter and within 8 weeks.

Efavirenz (SUSTIVA)
is the preferred
non-nucleoside reverse transcriptase inhibitor in patients on TB treatment starting ART

In cases of non-response
to TB treatment investigate the most likely alternate diagnosis: MDR-TB

about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Keith Alcorn, NAM's Senior Editor (London).

For further information please visit the HATIP section of aidsmap.com

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