FACTSHEET HIV and co-infections

Access for all must include access to everything

Whilst progress has been made to secure access to affordable antiretroviral (ARV) drugs for treating HIV, people living with HIV are still dying from preventable and curable co-infections. This factsheet highlights some of these co-infections and the barriers that prevent equitable access to innovative and quality-assured medicines.

Definition

Co-infections are generally defined as an infection with more than one disease at any given time.

Co-infections are more serious in people living with HIV because HIV weakens the immune system to the point where the body cannot fight off infections. Without treatment, people living with HIV can die from infections like tuberculosis, pneumonia and hepatitis C.

Tuberculosis

Tuberculosis is primarily an airborne infectious disease that usually attacks the lungs, but can occur in any part of the body. Tuberculosis can infect anyone, anywhere. **Nearly nine million people developed TB and 1.5 million died from it in 2013**, despite the disease being both curable and preventable.[1] Worldwide, TB is the leading cause of death among people living with HIV and causes one fifth of all HIV-related deaths. The most recent figures estimates that **1.1 million TB patients are co-infected with HIV** and an estimated **360,000 people die of HIV-associated TB annually**.[2] Due to a weakened immune system, in any single year a person with HIV and latent TB has a one in ten chance of developing active TB. Africa bears a disproportionate burden of TB/HIV co-infection and accounts for three quarters of all TB patients who are co-infected with HIV.

The TB access challenge

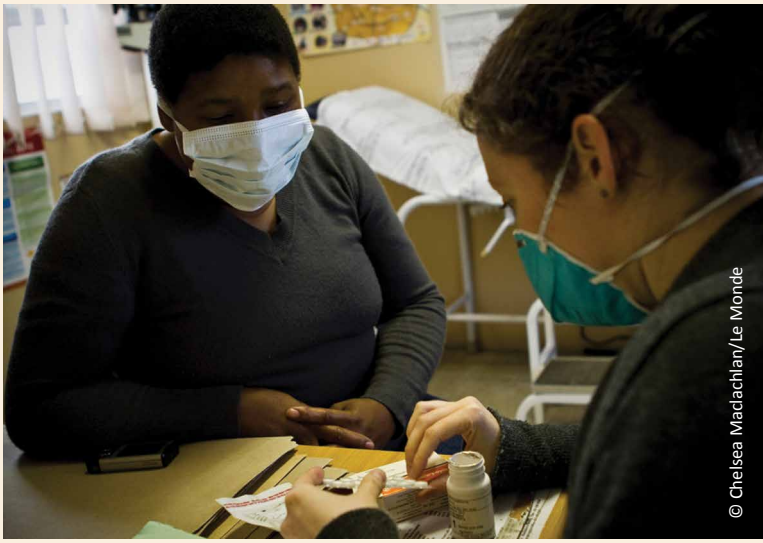
- As those affected by TB are overwhelmingly the world's poor there has been no profit-incentive to develop new treatments. Decades of under investment in research and development (R&D) for new tools to fight TB have seriously hampered the fight against the disease. There has only been one new FDA approved drug in 50 years, meaning that treatment for drug sensitive TB is long and arduous, lasting a minimum of six months.
- There is an alarming increase in the number of TB patients with drug-resistant strains. Treatment for multi-drug resistant TB (MDR-TB) is only effective about half of the time, lasts a minimum of 18 months and causes serious side effects including permanent and complete hearing loss. It is often not available or is far too expensive for patients – priced between 50 and 200 times standard TB treatment. Two new drug resistance (DR) TB drugs, delamanid and bedaquiline, are coming online (bedaquiline was approved for MDR-TB in 2012 and delamanid in late 2013) but this is way short of what is needed and high prices are likely to block access.
- Moreover, widespread drug stock-outs, the lack of an effective vaccine, the lack of a rapid diagnostic test suitable for rural contexts, and the lack of a test that accurately assesses all kinds of drug resistance are all further threatening TB care and control.
- HIV patients with TB are still being denied proper treatment and support. Drug interactions mean some ARVs are less effective when taken at the same time as key TB medicines. New ARV-compatible TB drugs are badly needed. Furthermore, despite the increased risks, people living with HIV are often still not receiving consistent TB screening and only about a third of the 1.6 million people newly enrolled in HIV care are receiving drugs that can help to prevent active TB.[3]

Action needed

- **A significant increase in investment to incentivise R&D for new TB treatments is urgent and essential.** Even for the two new treatments, trials demonstrating how they should and shouldn't be combined in the regimens we require to effectively tackle TB are still not underway. Support for an open collaborative R&D approach that incentivises research organisations to share scientific data and clinical trial results as early as possible and to conduct medically appropriate research on combinations of compounds is needed to radically ramp up innovation and deliver affordable new treatments. There will never be the reward of big, patent monopoly-protected sales to encourage pharmaceutical sector investment in TB research. The UK and others must support alternative approaches that use grant and prize funds to drive research like Médecins Sans Frontières' (MSF) Push, Pull, Pool proposal.
- **The prices of new treatments must be affordable**. The only proven and sustainable means of achieving that is through the facilitation of generic production and the availability of those quality-assured generic drugs in all low- and middle-income developing countries.
- **There is an urgent need for a simple, affordable and easy to use point of care diagnostic test**. A new diagnostic test, GeneXpert MTB/RIF, is helping to improve the diagnosis of TB in people who live with HIV but there is a need for one that can deliver results on the spot in resource-limited and remote settings and that can test for drug resistance beyond rifampicin.

Case Study: HIV/TB MSF Khayelitsha

South Africa has been particularly hard hit by HIV/TB co-infection with 62% of newly diagnosed TB cases in 2012 co-infected with HIV. Significant strides have been taken across the country to address this problem. In Khayelitsha, a township 30 kilometres outside of Cape Town, service providers, including the Department of Health and Médecins Sans Frontières, have been scaling up HIV/TB/MDR-TB integration. Co-infected patients are now able to receive their treatment in the same clinic, and often from the same provider; the time from the start of TB treatment to ART initiation has significantly decreased; nurses' clinical skills in managing both diseases has improved; and patient support strategies targeting retention in care, viral load suppression, and TB treatment success have been integrated for co-infected patients. The scaling up of TB-HIV integration in Khayelitsha, including decentralised primary care for HIV, TB and MDR-TB, has had a tangible impact on the lives of thousands of people living with HIV and TB, decreasing rates of both illness and death among people living with HIV.



Vanelwa (who has HIV/DR-TB co-infection) has a consultation at the MSF-supported Ubuntu clinic in Khayelitsha, Cape Town.

Hepatitis C

Approximately 185 million people are infected with HCV globally, with 150 million of those chronically infected. The majority of chronic cases are concentrated in middle-income countries. It is estimated that 350,000 million people die every year due to HCV-related liver complications. The old standard of care is a combination including injectable peg-interferon. The cure rate is 50–75% and only 30–60% for patients living with HIV and is associated with strong side effects. Plus, it is very expensive. Worldwide, only a tiny percentage of people with HCV have access to treatment.[4]

New direct acting antivirals (DAAs) for HCV hold the promise of revolutionising treatment. All-oral combinations of these DAAs are leading to cure rates in the mid-90% range. Treatment duration is shorter, 8–24 weeks, and the drug is better tolerated.

HCV access challenge

Prices charged for the first of these DAAs, Gilead's sofosbuvir, are extremely high in the developed world – $84,000 for a 12-week course in the US. The drug made more money in its first quarter of sales than any drug in history. Gilead have signed voluntary licence agreements with seven generic manufacturers but these deals largely exclude the middle-income countries where over 70% of those affected live. There, Gilead are implementing a tiered pricing approach where the price will be negotiated on a country-by-country basis, which will likely result in continued unaffordability of HCV treatment. Furthermore, many access to medicines experts from across civil society fear that the voluntary licences agreed by generic manufacturers with Gilead will prevent them selling to countries outside the agreement even if such sales are completely legal. It has been estimated that generic competition could drive the price to $135 in the medium-term.[5] Gilead's patent on sofosbuvir is being challenged in India. If overturned it could pave the way for much broader availability of generic sofosbuvir.

Bristol Meyers Squibb (BMS) have also launched a HCV treatment, daclatasvir, which works in combination with sofosbuvir, pushing cure rates to 100%. BMS have been heavily criticised for refusing to allow any generic production.

The Global Fund to Fight AIDS, Tuberculosis and Malaria, one of the few organisations with the global scope to effectively tackle HCV amongst people living with HIV, has discussed revising its position to prevent countries paying for HCV treatment through their grants. It would be deeply regressive and damaging for the Global Fund to make such a move and would jeopardise the lives of key population groups, particularly people who inject drugs, across the world.

Action needed

- **Swift acceleration of access to affordable generic DAAs for HCV should be prioritised** to ensure all those living within the geographic scope of licence agreements can access affordable treatment.
- **Countries excluded from voluntary licence deals should use the legal flexibilities within TRIPS to issue compulsory licences** for sofosbuvir and generic manufacturers should prioritise public health by supplying them.
- **Countries, implementers and donors must prioritise HCV programming** that includes support for diagnosis and treatment without out-of-pocket costs for patients.
- **The Global Fund should conclusively state that it exists to fund the response to the three diseases wherever it is required**, including treating the infections associated with HIV such as HCV, giving implementer countries the power to determine the most effective use of the investment from the Fund.
- **Improved harm reduction services for countries with HCV epidemics** affecting people who use drugs, including needle exchange and opioid substitution therapy.
- **Normative and country guidelines should include screening for higher risk groups**, including those living with HIV.

Visceral leishmaniasis

Visceral leishmaniasis (VL), also known as kala azar, is a neglected tropical disease caused by different species of the *Leishmania* parasite and is transmitted through the bites of sandflies. VL is endemic in large parts of Sudan and South Sudan as well as areas of Kenya, Ethiopia and Somalia and is deadly if left untreated.

VL interacts with HIV and co-infection is common in East Africa. North-western Ethiopia has the highest burden of VL/HIV co-infection where between 25 and 41% of VL patients are co-infected with HIV.[6] VL is an AIDS-defining condition and is an indication for starting ART irrespective of the patient's CD4 count.[7] For many HIV-positive patients VL cannot be fully cured, even after extensive anti-leishmanial treatment.[8] Co-infection is therefore often an almost untreatable mix that results in repeated relapses, increased drug unresponsiveness, and eventually death, even if treatment for both infections can be accessed.

The interaction of VL with HIV adds considerable complexity to the treatment of both diseases. Risks are increased: HIV and *Leishmania donovani* both attack the cellular immune system and reinforce each other in a detrimental manner. Because of the much higher parasite burden in their body, VL/HIV co-infected patients are important reservoirs for disease transmission. Response to HIV treatment is impaired as co-infected patients respond less well to ART.[9] At the same time treatment of VL is less effective in HIV-positive patients, has higher drug toxicity and higher mortality.

The VL access challenge

- Existing treatments have an unacceptably high mortality rate due to toxicity or low levels of effectiveness in co-infected patients in East Africa. Better high-dose combination treatment regimens therefore need to be developed. Initial results of a recent MSF study suggest new drug combinations significantly improve outcomes in HIV-positive VL patients.[10] Further study on this combination therapy is planned.
- Access to the preferred treatment, liposomal amphotericin B (LAmB), is a major challenge, partly because of logistical issues – the drug needs to be transported by cold chain and stored at or below 25C – and partly because the price is too high for national control programmes. AmBisome, the LAmB drug produced by Gilead, is currently available at WHO-negotiated prices of $18 per vial. As more than 25 vials are usually necessary to treat co-infected patients, the cost per treatment course often exceeds $450. In addition, not all the drugs required to treat VL in HIV-positive people are available in endemic countries. The majority are not registered in East African endemic countries, limiting the capacity to import the drugs and therefore provide the needed treatment options to patients co-infected with HIV.

Action needed

- **Donors and national HIV programmes in VL-endemic countries should scale up prevention, diagnosis and treatment of VL**. Early diagnosis and treatment of VL patients saves lives and reduces disease transmission. In endemic areas, all HIV-positive people should be investigated for VL. Access to early ART for those most vulnerable to VL, including rural migrant labourers and resettled and internally migrated populations, should also be improved. VL should be included as an indication for initiation of ART, irrespective of CD4 count in ART guidelines in endemic settings. In HIV-positive patients who are infected by *L. donovani* but who have not developed VL, early use of ART may be the best way of preventing reactivation of latent VL as an opportunistic infection. This calls for the rapid implementation of WHO guidelines in favour of early initiation of ART (CD4<350/mm^3) in countries where VL is endemic.
- **Access to optimal treatment should be secured, Gilead, the manufacturer of AmBisome should reduce the price further**. The feasibility of developing quality assured alternative generic sources of liposomal amphotericine should be explored urgently. VL drug manufacturers should undertake registration in endemic countries, and endemic countries authorities should help to facilitate registration. Increased investment in research into prevention, diagnosis, treatment and secondary prophylaxis of this neglected opportunistic infection should be pursued.

Cryptococcal meningitis

Cryptococcal meningitis is the leading cause of adult meningitis in sub-Saharan Africa, and contributes up to 20% of AIDS-related mortality in low- and middle-income countries every year. Antifungal treatment for cryptococcal meningitis relies on three old, off-patent antifungal drugs – amphotericin B deoxycholate, flucytosine and fluconazole. Widely accepted treatment guidelines recommend amphotericin B and flucytosine as first-line induction treatment for cryptococcal meningitis. However, flucytosine is unavailable in Africa and most of Asia, and safe amphotericin B administration requires patient hospitalisation and careful laboratory monitoring to identify and treat common side-effects.[11]

While increased access to ART can lead to reduced incidence of cryptococcal meningitis, mortality linked to HIV-related cryptococcal meningitis remains unacceptably high across sub-Saharan Africa: in one setting in rural KwaZulu-Natal, South Africa, 41% of cryptococcal meningitis patients died in hospital within 30 days of admission.

The cryptococcal meningitis access challenge

The drugs required to treat cryptococcal meningitis are prohibitively expensive and vulnerable to stock-outs, as happened in South Africa in 2011 due to a worldwide shortage. Liposomal amphotericine, sold as AmBisome by Gilead, is sold in the private sector in South Africa at not less than $243 per vial, making it prohibitively expensive for application in the public sector.

Action needed

- **WHO recommended treatments should be registered and made available** in all countries.
- **Generic production of liposomal amphotericin B is required** to ensure its affordability and application in the public sector.

Cytomegalovirus (CMV) retinitis

CMV is often contracted at a young age and is considered benign if a person has a well functioning healthy immune system. However, CMV becomes activated when a person has a severely compromised immune system, as seen in advanced HIV. More often than not, CMV attacks the retina but it can also infect other organs, such as the lungs and the oesophagus. If left untreated CMV can lead to loss of vision in one or both eyes, causing permanent blindness. With the arrival of ART in the 90s, CMV retinitis went from a widespread disease to a virtually non-existent one among people living with HIV in developed countries. Unfortunately, many people living with HIV in developing countries remain undiagnosed and untreated until the disease has reached advanced stages and considerably compromises the immune system. According to a recent study, the highest prevalence of CMV retinitis is in Asia, where 14% of cases are thought to be located.[12] Over 70% of

people living with HIV diagnosed with CMV disease were reported to have a CD4 count of less than 50 cells/µl at the time of the diagnosis.

The CMV access challenge

- **Diagnosis of CMV retinitis**: Adequate ocular screening for CMV retinitis requires medical practitioners to be trained in retinal examination such as direct or indirect ophthalmoscopy. In regions with high disease burden, few HIV clinicians are skilled in such techniques and trained ophthalmologists are scarce.
- **Treatment of CMV retinitis**: The current most widely used methods of treatment for CMV retinitis are intravenous and intraocular injections of ganciclovir. Intravenous injections are logistically challenging, as they demand that the patient stays at a well-staffed clinic or hospital for the entire duration of the treatment. Intraocular injections consist of injecting ganciclovir directly into the infected eye multiple times. While this method of treatment may effectively cure the infected eye, it will not be effective on other potentially CMV-infected organs. The medical procedure itself is likely to be a traumatic experience for the patient. The treatment also requires going to the health centre weekly, which may be logistically and financially difficult for patients and their families in resource-limited settings. The treatment that would solve the problems encountered by patients with other methods of treatment is the drug valganciclovir. Being an oral drug with the same efficacy as injections makes valganciclovir a highly appealing option, not only for treating CMV retinitis in both eyes but also other infected organs altogether. While it is widely available in developed countries, valganciclovir is unfortunately out of reach for those most in need of treatment because of unavailability, high prices and a lack of generic suppliers.

Actions needed [13, 14]

- **Screening for CMV retinitis among first-time presenters for HIV with CD4 counts below 100 cells/µl would enable early detection and treatment.** Clear WHO guidance is required as well as inclusion of CMV screening in national HIV programmes as a routine test in HIV care. HIV specialists in resource-limited settings should be trained in techniques to accurately examine the eye for this condition.
- **Access to valganciclovir to treat CMV retinitis should be improved in developing countries** through inclusion of treatment guidelines at an international and national level, and reduced treatment prices. In August 2013, the patent holder, Roche signed an agreement with the Medicines Patent Pool (MPP), allowing valganciclovir to be sold at a discount of up to 90% in 138 low and middle-income countries. The price discount will be followed by a license agreement enabling generic entry.
- **Recent inclusion of valganciclovir in the list of products that can receive quality assurance under the WHO Prequalification of Medicines Programme** may pave the way for entry of generic manufacturers. This will lead to competition with one another to make valganciclovir available at low prices.

Conclusion

Across all these co-infections, global efforts are falling short and significant legal and structural barriers are undermining public health and the HIV response. Unless the actions detailed here are fully implemented – from securing generic production, reforming programmatic delivery and establishing a new public health driven approach to R&D – the effort to begin the end of the AIDS epidemic will be fatally undermined.

Endnotes

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