MSF Access Campaign
Technical Briefing Document
JULY 2018

Stopping Senseless Deaths

Overcoming access barriers to affordable, lifesaving diagnostics and treatments for HIV and opportunistic infections

Introduction

The world is working towards achieving the 90-90-90 HIV treatment targets by 2020. In 2017, more people than ever – 21.7 million of the world's 36.9 million HIV-positive people – were receiving antiretroviral treatment (ART).[1] Yet there are persistent – and deadly – gaps in the global response to HIV/AIDS that undermine progress against the epidemic: 25% of people living with HIV do not know their status and only 59% are receiving ART.[1] Millions of people still remain at risk for opportunistic infections (OIs) and death.

In 2017, 940,000 people died from HIV/AIDS-related illnesses.[1] These senseless deaths are occurring among people who interrupted treatment or were diagnosed with HIV and OIs when they were already too ill to benefit from ART.

ART coverage among children living with HIV is unacceptably low, and their treatment options are suboptimal. In 2017, only 52% of HIV-positive children were receiving treatment.[1] As a result, the death rate among HIV-positive children, especially during their first four years of life, remains high. In 2017, 110,000 children died from AIDS-related illnesses.[2]

Zipporah, from Homa Bay, Kenya, is 33 years old. After testing positive for HIV, she delayed starting ART because she was afraid of the treatment. She has Kaposi sarcoma and will start chemotherapy soon. In Homa Bay hospital, MSF supports the Kenyan Ministry of Health in providing comprehensive HIV services, including specialised hospital care for AIDS.

This technical brief analyses access barriers to affordable, lifesaving diagnostics and treatments for HIV and OIs, including adult and paediatric formulations of dolutegravir – a highly effective and tolerable HIV integrase inhibitor that replaces efavirenz in first-line treatment regimens. Updated antiretroviral (ARV) drug pricing information is also provided (see Annex 1).

Advanced HIV disease

The World Health Organization (WHO) defines advanced HIV disease among adults or adolescents as a CD4 cell count of <200 cells/mm^3 or a WHO clinical stage 3 or 4 event. All HIV-positive children under five years of age are considered as having advanced HIV disease.[3]

In recognition of the need for improved prevention and treatment of advanced HIV disease, the WHO issued its first guideline for the management of people with advanced HIV disease in 2017, defining a package of interventions aimed at reducing morbidity and mortality.[3]

Although AIDS-related mortality has decreased over the last decade, the annual number of deaths due to AIDS has declined only minimally since 2014,[1,4,5] – driven by delayed diagnosis, treatment interruptions and virologic and immunologic failure among HIV-treatment-experienced people. Since 2010, the proportion of people who present for care with advanced HIV disease or AIDS has not changed.[6] In low- and middle-income countries (LMICs), 30–40% of people present for care with advanced HIV disease or AIDS.[3,7,8] These immunosuppressed adults and children are at high risk for deadly OIs, such as tuberculosis (TB), cryptococcal meningitis (CM), Kaposi sarcoma (KS), toxoplasmosis, *Pneumocystis* pneumonia (PCP), severe bacterial infections (SBIs) and death, even after starting ART – especially people who have a CD4 cell count of <100 cells/mm^3.[9,10,11]

Advanced HIV disease in HIV treatment-experienced patients

The burden of advanced HIV disease is shifting away from late presenters and newly diagnosed people who are entering care to people who have interrupted ART, or remained on ineffective ART. In South Africa, where ART coverage increased 30-fold between 2005 and 2016,[7,12] an alarming trend is emerging. Over a 10-year period, the proportion of ART-naïve patients entering care with a CD4 cell count of <50 cells/mm^3 has decreased, from 60.9% to 26.7%, while the proportion of ART-experienced patients returning to care with <50 cells/mm^3 rose – from 14.3% to 56.7%.[13] A survey of hospitalised patients with advanced HIV disease who had received ART for >6 months in Kenya and the Democratic Republic of Congo reported CD4 cell counts of <100 cells/mm^3 among 45.8% (152/331) of people, and HIV RNA >1,000 copies/mL among 67.2% (252/376) of people.[14]

HIV/AIDS in West and Central Africa

Progress against AIDS lags most in West and Central Africa, where 30% of global AIDS-related deaths – and 40% of AIDS-related deaths among children – occur.[15] The region is home to 6.1 million HIV-positive adults, adolescents and children. In 2017, only 41% of adults and adolescents and 26% of children in West and Central Africa were accessing ART, with a 29% rate of viral suppression.[16]

CD4 testing – the gateway to identifying advanced HIV disease

Although current WHO guidelines no longer recommend CD4 testing to initiate ART and monitor people's response, it remains essential for identifying patients with advanced HIV disease.[17] It is important to maintain access to and capacity for CD4 testing[18] since it is the gateway to identifying patients who need rapid reflex testing for OIs.

The current expansion of access to HIV testing outside of health facilities[19] could also include CD4 cell testing to identify people with advanced HIV disease. A simple, disposable lateral flow assay that measures CD4 in a fingerprick of blood would facilitate expansion of CD4 testing to community-based settings and remote areas.

The VISITECT CD4 assay from Omega Diagnostics was launched in April 2018, shortly after receiving CE-mark approval.[20] It is the first semi-quantitative CD4 lateral flow assay, and meets all WHO ASSURED criteria (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users),[21] but the current version has a CD4 threshold of 350 cells/mm^3. The company is currently developing a new version that has a CD4 threshold of 200 cells/mm^3 and could identify people with advanced HIV disease in less than an hour. The first prototype has undergone preliminary evaluation at the National Health Laboratory Service CD4 reference laboratory in Johannesburg, South Africa. Initial results are encouraging, and further test optimisation and field evaluations are expected to

start in 2018. In the meantime, the WHO, in collaboration with other stakeholders, is developing a target product profile to guide CD4 diagnostics manufacturers.

Resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs)

To prevent treatment failure, advanced HIV disease and death, the WHO recommends changing first-line ARVs when the national prevalence of pre-treatment HIV drug resistance exceeds 10%.[22]

The effectiveness of NNRTIs, which are used in most LMICs as part of first-line treatment, is compromised by transmitted or acquired drug resistance. In LMICs, where only 50% of people have access to routine viral load monitoring,[23] the incidence of NNRTI resistance is increasing.[22, 24] People who have already been exposed to, or are resistant to, these drugs may be initiating, remaining on, or re-initiating an NNRTI-containing regimen, which puts them at risk for HIV treatment failure, advanced HIV disease or AIDS, and death.[22,24] Given the increase of NNRTI resistance, viral load monitoring is essential for identifying HIV treatment failure and triggering a switch to effective second- or third-line ARVs to prevent or treat advanced HIV disease or AIDS.

Dolutegravir (DTG) for Adults

The HIV integrase inhibitor DTG could optimise first-line ART. Because it has fewer side effects and a higher genetic barrier to resistance than efavirenz (EFV), it may even reduce advanced HIV disease prevalence by lowering rates of treatment discontinuation and treatment failure.[25] DTG's once-daily 50 mg dose has improved potency and tolerability, fewer drug interactions, and a higher genetic barrier to resistance than standard-dose (600 mg) EFV.[26] The low daily dose makes generic DTG easy to co-formulate into fixed-dose combinations (FDCs), and generic versions, where available, are affordable at US$75 per person, per year.[27,28] In 2015, WHO recommended DTG as an alternative first-line ARV, pending information on safety during pregnancy and TB treatment.[29] In 2018, interim data became available on co-administration of DTG with rifampicin in people with HIV/TB coinfection; a double dose of DTG (50 mg/twice-daily) was effective and tolerable during TB treatment.[30]

DTG for second-line treatment

The 2018 WHO HIV guidelines upgrade DTG-based regimens from alternative to preferred for first-line treatment, with a strong caution for women of child-bearing age to use DTG with effective contraception.[31]

New concerns for DTG use during early pregnancy

DTG has been used as part of first-line treatment in Botswana since 2016. In May 2018, the Botswana observational cohort reported neural tube defects – birth defects of the brain, skull, spinal cord and spine that may occur during the first four weeks of pregnancy – among 0.9% (4/426) of babies whose mothers were taking DTG when they became pregnant. This rate of almost 1 in 100 compares with approximately 1 in 1000 (0.1%, 14/11,173) among babies whose mothers took other ARVs when they became pregnant.[32] Data on safety of DTG when started later in pregnancy are reassuring.[33] The Botswana observational study is ongoing; more information on DTG use at conception and during pregnancy, from this and other cohorts, are expected in early 2019.

ViiV Healthcare, DTG's originator, did not find safety signals during their early toxicology and animal reproductive studies,[34] but these studies do not fully characterise drug safety at conception, during pregnancy and infant outcomes in humans.[35] Post-marketing surveillance, including pregnancy cohorts that collect data on timing of ART initiation and infant outcomes, should be conducted for DTG and all new ARVs, and national pharmacovigilance systems need to be strengthened.[36]

DTG should be available to all who need it, including women. Given the concerns around the neural tube defects safety signal, WHO recommends the consistent use of effective contraception for all women of child-bearing age receiving DTG-based treatment, or the use of an alternative ARV regimen that has demonstrated safety and efficacy.[37]

United Nations Population Fund (UNFPA) data from 2017 shows the world's highest unmet need for contraception is in sub-Saharan Africa, where use of any type of contraceptive ranges from 7% in South Sudan to 67% in Zimbabwe.[38] Countries, HIV programmes, and donors should seize this opportunity to improve access to effective contraceptive options such as intra-uterine devices, implants and injectables for all HIV-positive women who do not want to become pregnant, including those who are on, or wish to start, DTG-based treatment.

To reduce pill burden and side effects, DTG-based regimens for second-line treatment may be preferable to lopinavir/ritonavir-based second-line regimens. Data are needed to inform the use of DTG in second-line regimens, especially data to better understand the prevalence and clinical relevance of resistance to tenofovir (TDF) and lamivudine/emtricitabine (XTC) – the reverse transcriptase inhibitors (NRTIs) commonly used in first-line regimens – and to determine whether DTG could be used with the same NRTIs in first- and second-line treatment. Additional sequencing data are also needed to determine optimal second- and third-line treatment following DTG-based first-line treatment.

Adult DTG formulations

DTG is available as 50 mg tablets (Tivicay), and in an FDC of DTG with abacavir (ABC)/lamivudine (3TC) (Triumeq) from ViiV Healthcare.

WHO Prequalification Programme (WHOPQ)-approved generic versions of DTG 50 mg are available from Cipla and Aurobindo.[39] In August 2017, Mylan and Aurobindo received tentative approval from the USFDA for generic FDCs of TLD (TDF/3TC/DTG).[27,28] Generic TLD is or will be available in 92 LMICs for US$75 per person, per year.[40,41] Upper middle-income countries such as Belarus, China, Malaysia and Kazakhstan are not included in the ViiV/Medicines Patent Pool (MPP) license territory and remain unable to access generic DTG.[42] In Belarus, the price of DTG alone is US$2,190 per person, per year.[43]

No DTG for children

The WHO 2018 HIV interim guidance includes a significant change in the recommendations for paediatric first-line treatment, from ABC or zidovudine (AZT) + 3TC and lopinavir/ritonavir (for infants and children under three years of age); EFV with ABC/3TC or AZT/TDF (for children three years to less than 10 years of age), and EFV with either TDF/XTC, AZT/3TC or ABC/3TC [44] to DTG/ABC/3TC as the preferred first-line regimen for children aged four weeks to 10 years of age.[31] Currently, there is no WHO dosing recommendation for DTG in children who weigh <25 kg; results from these ongoing studies are also needed to inform dosing for a DTG-based FDC for children. Forty per cent of children who are on HIV treatment continue to receive sub-optimal nevirapine-based regimens, putting them at risk of increased side effects, resistance and treatment failure, thereby increasing their risk of contracting opportunistic infections and dying.[45]

ViiV Healthcare makes paediatric formulations of DTG in 10 mg and 25 mg tablets, and has a 5 mg dispersible tablet that is still in development. In 2013, ViiV was lauded for developing a royalty-free voluntary license (VL) with the MPP for its paediatric DTG. The VL covers more countries than any other MPP license with a pharmaceutical company. [46] Since then, ViiV has registered paediatric DTG formulations in the EU and the US; however, they are unavailable in most LMICs (ViiV has only started the registration process in three sub-Saharan African countries).

Despite repeated requests and recommendations to accelerate access for children from WHO's Paediatric Antiretroviral Drug Optimization group and the Paediatric HIV Treatment Initiative[47,48], and despite ViiV's public commitment at the 2017 High Level Dialogue on Ending AIDS among Children and Adolescents, [49] the company has not disclosed its registration plans for paediatric DTG and has still not filed to register the 5 mg dispersible tablet – effectively delaying development of generics. Worse, though the practice is both legal and common, ViiV refuses to allow importation of existing paediatric DTG for programmatic use via importation waivers in countries where it is not registered or where registration is pending.

In July 2018, Unitaid, the Clinton Health Access Initiative and ViiV announced the launch of a partnership to support generics manufacturers Mylan and Macleods to develop, manufacture and supply generic formulations of paediatric DTG.[50] This is a step in the right direction, but since it can take several years to develop and register generic medicines, the global HIV community remains dependent on ViiV to supply paediatric DTG for the foreseeable future.

Opportunistic Infections (OIs)

Tuberculosis (TB), cryptococcal meningitis (CM), *Pneumocystis* pneumonia (PCP), Kaposi sarcoma (KS), severe bacterial infections (SBIs) and cytomegalovirus (CMV) are the leading causes of illness and death among people with advanced HIV disease.

Diagnostics for overlooked OIs

There is insufficient investment in – and availability of – affordable, quality-assured, accurate, and user-friendly diagnostic tools suited to resource-limited settings, including for important advanced HIV- and AIDS-related OIs. As a result, information on the burden of OIs among people living with HIV in

LMICs remains limited, and often go undiagnosed. Table 1 describes the main access barriers to implementation of diagnostics to facilitate advanced HIV disease management in resource-limited settings.

Table 1: Access barriers to OI diagnostics in resource-limited settings

Indication	Test	Facility level	Barriers
CMV	Eye examination Molecular method	Clinic Laboratory	• Lack of trained healthcare workers to perform eye examination (binocular indirect ophthalmoscopy) • Lack of standardised and commercial molecular methods • High cost of molecular methods
KS	Histopathology X-ray	Specialised laboratory	• Lack of histopathology laboratory infrastructure, quality-assurance and human resources
PCP	Microscopy Molecular method	Specialised laboratory	• Lack of reagents and training in microscopy • Lack of standardised molecular methods • High cost of molecular methods
SBIs	Blood culture Molecular method	Specialised laboratory	• Lack of political commitment to install microbiology laboratories • Lack of laboratory infrastructure, equipment, logistics, quality-assurance and human resources • High cost impedes large-scale implementation
Toxo-plasmosis	Serology (IgG-IgM) Molecular method CT scan	Clinic Laboratory	• Lack of quality-assured antibody-based rapid diagnostic tests • Lack of standardised and commercial molecular methods • High cost of molecular methods • CT scans are rarely available

Tuberculosis

Globally, TB is the leading cause of death – and a leading cause of hospitalisation – among people living with HIV.[3] In 2016, 374,000 HIV-positive people died from TB coinfection, and an estimated 1.4 million people were living with HIV/TB coinfection.[51]

As of 2017, more than 15 million HIV-positive people did not have access to ART, leaving them vulnerable to active TB disease, illness and death.[1] Latent TB infection (LTBI) is ten times more likely to develop into active TB disease in HIV-positive people who are not receiving ART. [52] When untreated, HIV and TB worsen each other, hastening progression of each disease.

TB diagnostics

Since 2010, WHO has recommended molecular tests, such as Xpert MTB/RIF (and, since 2017, the newer Xpert Ultra), for initial TB testing and detection of rifampicin resistance in people living with HIV.[53,54,55] The tests are included in the package of care recommended for people with advanced HIV disease,[3] but despite inclusion in national guidelines, implementation of, and access to, Xpert MTB/RIF has not been brought to scale in many countries.

A 29-country survey conducted in 2017 reported that 95% of included countries had national policies recommending Xpert MTB/RIF as the initial TB test for HIV-positive people, but only 50% were widely implementing it.[56] Systems-, operational-, provider- and patient-level barriers to implementation and uptake of Xpert MTB/RIF include: lack of integrated TB/HIV programmes and services; high cost for the machine and cartridges (discounted in 145 LMIC/ high-burden countries to US$17,000 for the machine and US$9.98 per cartridge); poor supply chain management; interrupted electricity; lack of knowledge and training; difficulty in collecting sputum samples, and lack of access to off-site testing.[56,57,58]

TB is harder to diagnose in HIV-positive people. Over 50% are sputum smear negative, since they

may either have low sputum bacillary loads or be too ill to produce sputum, and because they are more likely to have extrapulmonary TB (especially when CD4 cell count is <50 cells).[59,60]

TB-LAM is a lifesaving rapid (<30 minutes), inexpensive (US$3.50), point-of-care urine test that detects lipoarabinomannan (LAM), a marker of active TB disease and increased risk of mortality among HIV-positive people.[61]

In 2015, WHO recommended TB-LAM to help diagnose TB in HIV-positive adults with a CD4 count ≤100 cells/mm^3 or those who are seriously ill, regardless of CD4 count;[62] it is included in the package of care recommended for people with advanced HIV disease.[3] Since then, numerous reports have identified benefits of TB-LAM testing in ambulatory and hospitalised patients with CD4 counts of ≤200 cells/mm^3, including reduction in 8-week mortality in two randomised controlled trials;[63,64] same-day results, facilitating rapid treatment initiation for patients at high risk of death; increased diagnostic yield; diagnosis of unsuspected TB infections; and TB diagnosis among sputum-scarce patients.[65,66,67,68,69,70]

Despite its usefulness, TB-LAM is not widely recommended in national treatment guidelines, preventing implementation where it is needed. A 29-country survey conducted in 2017 reported that TB-LAM was only included in guidelines in two countries.[56]

TB prevention

TB is preventable, both with ART and isoniazid (INH). ART reduces the risk of TB by 65% at any CD4 cell count,[71,72] highlighting the need for continued ART scale-up for the 15.2 million people who were without access to treatment in 2017.[1]

TB preventive treatment is part of the package of care for adults, adolescents and children with advanced HIV disease.[3] Since 1998, WHO has recommended preventive treatment for all HIV-positive people who do not have signs and symptoms of TB disease.[73] Treating LTBI with INH reduces the risk for active TB disease in HIV-positive people by 35%.[74] Yet in 2016, only 42% (940,269/2,263,682) of people who were newly enrolled in HIV care received TB preventive treatment.[51]

In 2018, WHO issued new guidelines for management of LTBI in countries with a high TB incidence, updating recommendations to include the options of three months of daily preventive treatment with rifampicin and INH for children and adolescents aged <15 years, and three months of weekly preventive treatment with rifapentine and INH (3HP) for both adults and children.[75]

Although rifapentine is not under patent, it is currently not co-formulated with INH. 3HP is weight based, and a typical adult dose, including vitamin B6 to prevent INH-related neuropathy, is 11 pills.[76]

The Global Drug Facility (GDF) lists a 3-month course of 3HP for US$45, which is relatively expensive (due to rifapentine pricing, which alone is listed at the same price from GDF[77]). Without a significant price reduction, implementation and scale-up of 3HP will be challenging. More research is also needed to determine how many times the 3HP regimen can be used to maintain prevention of TB. Although rifapentine can be used with TDF/XTC/EFV, it may interact with HIV protease inhibitors;[78] a small pharmacokinetic study on interactions between HP and dolutegravir found decreased DTG exposure, and was discontinued due to drug toxicity. Limited data are available on interactions between DTG and rifapentine.[79]

In the future, the duration of preventive TB treatment might be shorter. Results from ACTG A5279, the BRIEF TB trial, compared one month of daily rifapentine (450–600 mg) and INH (300 mg), called 1HP, to nine months of INH (9H) among 3,000 HIV-positive adults and adolescents >13 years in countries with a high TB burden. The incidence of active TB and death from TB or other causes did not differ; 1HP was as effective as 9H, and had fewer side effects and a higher completion rate.[80]

Additional studies of 1HP are needed in children, adolescents and pregnant women to inform optimal use of this regimen.

Isoniazid is available for US$5.20 for nine months of treatment with 300 mg daily.[77] Cipla has developed Q-TIB, a WHOPQ-approved FDC of co-trimoxazole, INH and vitamin B6 to prevent TB and other opportunistic infections among people living with HIV. In LMICs, Q-TIB is priced at a US$1.99 per month.[81]

TB treatment

ART has improved survival during treatment for coinfection with TB, including its drug-resistant (DR) forms,[82] but DR-TB patients, including those living with HIV, need access to shorter, more effective and less toxic DR-TB treatment. Access to bedaquiline and/or delamanid, newer TB medicines

that are urgently needed to treat multi-drug resistant (MDR) forms of TB, remain unacceptably limited; only 12% of those who needed them had access in 2016. Data to inform broader guidelines for their use is pending from ongoing studies, and barriers such as lack of registration and high prices continue to limit access.

The Johnson and Johnson (J&J) donation program for bedaquiline ends in March 2019. MSF is concerned that J&J will set a price for bedaquiline that will not allow for affordable access to efficient DR-TB regimens in LMICs. J&J's tiered pricing for a 6-month treatment course has been US$900 for low-income countries, US$3,000 for middle-income countries and US$30,000 for high-income countries. Otsuka charges US$1,700 for a 6-month supply of delamanid in Global Fund-eligible countries that procure the drug via the Stop TB Partnership's Global Drug Facility.

In the meantime, results from operational research and clinical trials of regimens that included at least one of these newer drugs in people with HIV/MDR-TB coinfection are promising. By December 2016, the ongoing NIX-TB trial had enrolled 61 people; 79% had extensively-drug resistant (XDR) TB and 49% were coinfected with HIV. After six months of treatment with bedaquiline, pretomanid and linezolid, all of the surviving patients were culture negative (there were three deaths from multi-organ TB and one from gastrointestinal bleeding). Final results are expected in 2018.[83]

Interim data are available from MSF-supported projects that have been treating 28 people for MDR-TB under routine programmatic conditions – including 11 HIV-positive people – with the combination of 6–12 months of bedaquiline and delamanid as part of individualized multi-drug regimens. After six months of treatment, 22/26 patients were culture negative, one patient died and one was lost to follow up. Overall, 19 of 26 patients maintained the combination of bedaquiline and delamanid as part of their treatment for more than 6 months, supporting the safe use of this combination in people with urgent need while larger trials are underway.[84]

Cryptococcal meningitis (CM)

Because many people still present for, or re-enter care with advanced HIV disease, CM remains a common – and deadly – opportunistic infection. It is the second most common cause of death among people with AIDS, accounting for 15% of global AIDS-related mortality. People with a CD4 count of <100 cells/mm^3 are at risk for CM, especially if they are not receiving ART or are on a failing treatment regimen.

An estimated 70% of people who are cryptococcal antigen (CrAg)-positive will develop cryptococcal meningitis unless they receive ART or fluconazole; the likelihood of progression among people who do not receive either intervention is 95%.[85] Annual prevalence of CM among people with advanced HIV disease or AIDS is estimated at 223,100; sub-Saharan Africa is home to 73% of cases. Each year, an estimated 181,000 HIV-positive people die from CM; 135,000 of these deaths in sub-Saharan Africa.[85]

In low-income countries, the estimated 1-year mortality rate from CM ranges from 70% among people who are in care to 100% among people who are not receiving treatment for HIV or CM, reflecting the lack of access to diagnosis and treatment.[85]

CM diagnostics

Screening and diagnosis of CM is done through cryptococcal antigen (CrAg) testing, which the WHO recommends for all HIV-positive people with low CD4 counts (<100 cells/mm^3 at ART initiation or re-initiation), and recommends should be considered for people with a CD4 count of <200 cells/mm^3.[86] CrAg can be detected in the blood weeks or months prior to the onset of clinical symptoms, which is useful as a screening test to guide prophylactic treatment. A faster, more accurate, less expensive (US$2.95) and simpler point-of-care (POC) test, the cryptococcal antigen lateral flow assay (CrAg LFA, IMMY, USA)[87], was recommended by WHO in 2011.[88]

CrAg testing could help drive implementation of widespread screening for, and pre-emptive treatment of CM, since the test works on whole blood and provides results in ten minutes. Although the test has been incorporated into HIV treatment guidelines in over 20 countries,[89] uptake has remained very low, partly due to limited availability of CD4 testing to identify patients with low CD4 cell counts.

Additional CrAg LFAs have recently become available. These include the Biosynex CryptoPS (Biosynex, France),[90] the StrongStep Cryptococcal Antigen Rapid Test Device,[91] and the FungiXpert (Genobio Pharmaceutical, China).[92] The Biosynex CryptoPS is a new LFA that may be useful to guide treatment as it detects low or intermediate levels of antigens in whole blood. Although initial results look encouraging, further evaluation is needed to validate the test in cerebrospinal fluid and whole blood with low concentrations of antibodies.[93,94]

CM prevention

CrAg screening is WHO-recommended for all HIV-positive adults and adolescents with a CD4 count of <100 cells/mm^3. If CrAg screening is unavailable, or the result is positive, WHO recommends primary prophylaxis with fluconazole for people with <100 cells/mm^3 prior to starting or re-starting ART, and to

consider fluconazole prophylaxis for people with a CD4 cell count of <200 cells/mm^3. [88]

CM treatment

Despite the prevalence of, and mortality from CM, old, toxic and expensive drugs are still used to treat the disease. The 2018 WHO cryptococcal disease guidelines recommend a 1-week induction phase of IV treatment with conventional (AmphoB) or liposomal (L-AMB) amphotericin B and oral flucytosine (5-FC), followed by a week of high-dose oral fluconazole, then eight weeks of lower-dose oral fluconazole as the preferred regimen for treating CM.[88] Although all of these drugs are off patent, access in LMICs remains limited. Often, the only option is monotherapy with fluconazole, which is suboptimal; 50-60% of people die after 10 weeks of treatment.

Pneumocystis pneumonia (PCP)

PCP remains a frequent cause of hospitalisation and death among patients with advanced HIV disease or AIDS in LMICs.[95] People with a CD4 count of <200 cells/mm^3 are most at risk.[95] Each year, at least 400,000 new cases of PCP occur among people with advanced HIV disease or AIDS;[96] the lack of diagnostic facilities leads to underreporting in LMICs.

PCP diagnostics

There are no specific signs and symptoms of PCP and it remains clinically challenging to identify the disease at an early stage. People usually present with shortness of breath, fever and a non-productive cough. *Pneumocystis jirovecii*, which causes PCP, cannot be cultured, so diagnosis relies on microscopy, histology, serology or DNA molecular testing, but these methods are typically unavailable in resource-limited settings because they are expensive and require extensive training.[95]

CM treatment is within sight, but out of reach for LMICs

Although 5-FC is included in all WHO-recommended treatment regimens for CM, neither the originator (Valeant, which sells a 2-week treatment course in the US for US$28,000) [97] nor generics producers who supply the US have taken steps to register 5-FC in LMICs. Mylan – the company with the largest share of the ARV market in LMICs[98] – purchased Meda, which was supplying generic 5-FC in France for US$63 per bottle[99] in 2016,[100] and raised the price to US$110 per bottle. Mylan has received WHOPQ approval for 5-FC 500 mg tablets,[101] yet it has not filed to register 5-FC in any sub-Saharan African country. Mylan could expedite registration via the WHOPQ Collaborative Registration Procedure to facilitate 5-FC procurement by countries where it is urgently needed.

Amphotericin B is used with 5-FC for the first 1–2 weeks of treatment. It comes in two forms, Ampho B, and L-AMB, a liposomal formulation. WHO guidelines indicate a preference for L-AMB, given its equivalent efficacy rates and better safety profile, although recognising that it is largely unavailable due to its high price.[88] Conventional AmphoB is sold in the private sector in South Africa for US$6 per vial[102]; it requires in-patient treatment and monitoring for changes in electrolytes and nephrotoxicity.

Gilead is the only source for quality-assured L-AMB, yet Gilead has not registered L-AMB in most LMICs. Under an agreement with WHO, Gilead makes L-AMB available to treat visceral leishmaniasis in selected high-burden countries at US$16.25 per vial, the company's stated at-cost price. Yet Gilead refuses to expand this pricing model to include a CM indication for LMICs, despite almost two years of requests from MSF and others. [103] In the private market in South Africa, for example, L-AMB sells at US$217 per vial[102], but is not available in the public sector. Although L-AMB is more expensive per vial than conventional treatment, if it were available at Gilead's at-cost price, countries could consider it as a treatment option. The entire cost of treatment must be considered, since L-AMB could reduce costs from side effects management, laboratory monitoring and hospitalisation (when patients can tolerate ambulatory care).

The ongoing AMBITION study is evaluating the treatment of CM with a one-time high dose of L-AMB in combination with 5-FC. Early results look encouraging;[104] if successful, this could reduce the cost of treatment and lead to more countries improving access.

PCP prevention

Early ART initiation prevents PCP. Primary prevention with co-trimoxazole prophylaxis decreases the risk of death from PCP by 19%–46% in LMICs.[105] Although co-trimoxazole is inexpensive and generally available in LMICs, it is used infrequently [106] due to implementation challenges such as irregular drug supply and stockouts.[107,108]

PCP treatment

High-dose co-trimoxazole is the recommended first-line treatment for PCP, but it can cause adverse events including renal impairment, gastrointestinal side effects, fever, and rash.[109] Severe cases of PCP may require intensive care services, which in-patient departments in resource-limited settings may lack.[14]

Kaposi sarcoma (KS)

KS is caused by the human herpes virus 8 (HHV8) and linked with both immunodeficiency and ongoing HIV replication.[110] It is the most common cancer among people living with HIV in Africa, including in children,[111] with the highest risk being among people with advanced HIV disease or AIDS. Without ART or chemotherapy, prognosis is based on tumour stage (whether KS is limited to the skin and/or lymph nodes, and/or minimal oral disease vs. tumour-associated oedema, ulceration, extensive oral KS, and KS in the gastrointestinal tract, lungs or liver) and presence of systemic disease (such as other OIs, fever, weight loss and diarrhoea).[112,113]

KS diagnostics

Adults with KS often have visible pale pink, purple or brown skin lesions, which can be painful as well as stigmatising; oral, genital or visceral KS may also be present. Children with KS are less likely to have skin lesions. Usually, KS is diagnosed clinically due to lack of laboratory infrastructure for performing biopsies and histopathology examinations, making it difficult to identify people who may benefit from chemotherapy.

KS prevention

ART is the most effective prevention against KS. ARV-associated viral suppression and immune reconstitution lower the risk for KS.

KS treatment

Current WHO advanced HIV disease guidelines do not include treatment recommendations for KS; it is important that they be included in their next update.

WHO recommends ART initiation for all HIV-positive people at any stage of KS. In people who have less extensive KS lesions on their skin, ART may cause regression but may not improve severe KS.[113] People who start or re-start ART with HIV RNA of >5 $\log_{10}$ copies/ml and a low CD4 cell count are at increased risk for KS-immune reconstitution inflammatory syndrome – and an abrupt worsening of existing KS, or unmasking of KS.[113,114,115]

WHO recommends chemotherapy for people with severe KS and disabling symptoms and recognises the need for additional research to inform optimal use of chemotherapy for HIV-positive people with KS.[113]

In high-income countries, the standard of care for KS is chemotherapy with pegylated liposomal doxorubicin (PLD) or daunorubicin. In LMICs, triple-therapy with conventional doxorubicin, bleomycin and vincristine is used, though often poorly tolerated. PLD monotherapy has fewer side effects and is more effective than triple therapy,[116,117] but access remains extremely limited in sub-Saharan Africa, mainly due to high prices and lack of registration.

KS treatment outcomes in Mozambique

In Mozambique, MSF supports a specialised HIV and KS treatment centre at the Centro de Referencia de Alto Maé in Maputo, where 1,210 patients were treated for KS between 2010 and 2015. Most patients had advanced HIV disease; 83% had severe KS. Most (78%) were treated with conventional triple therapy with doxorubicin, bleomycin and vincristine, which comes with poor outcomes and intolerable side effects (vomiting, bacterial superinfection, sepsis and neuropathy from vincristine). Half of the patients in this cohort were either lost to follow up or died.[118] In 2016, MSF introduced PLD as a pilot project at the same site, treating 116 people, for which interim results are encouraging. After six months, 55% were in partial or complete remission and 19% were lost to follow up or had died. The remaining patients were still on treatment.[119]

PLD is made by J&J and sold under the brand name Caelyx. In high-income countries, where the prevalence of KS is much lower, it is used largely for treatment of breast and ovarian cancers, at prices around US$1,000 per vial in the UK[120].

Two generics have been approved by the US Food and Drug Administration (USFDA), from Sun Pharma and Dr. Reddy's Lab, but they have not been registered in LMICs. Once they are registered, and can enter the market, generic products will hopefully bring about competition and reduced prices in LMICs. The best price for generic PLD is US$160 per vial. Treatment generally requires up to 12 vials (at an average two vials every two weeks).

PLD is not included on the WHO's Essential Medicines List (EML); it should be added to encourage its addition to national EMLs, and to accelerate uptake and access to affordable generic versions.

Severe bacterial infections (SBIs)

SBIs continue to cause illness and death among adults and children living with HIV, particularly Streptococcus pneumoniae, non-typhoidal strains of Salmonella enterica, Escherichia coli and Staphylococcus aureus.[121]

SBIs are a major cause of illness, hospitalisation and death among people with advanced HIV disease; [122] globally, a third of hospitalisations among HIV-positive adults and children result from SBIs, most commonly bacterial pneumonia, isolated bacteraemia and severe diarrhea.[122] The highest mortality rates are found among HIV-positive adults and children who are hospitalised for SBIs or AIDS-related infections.[122]

SBI diagnostics

Microbiological techniques are needed to accurately diagnose SBI, but access to clinical bacteriology laboratories in resource-limited settings is extremely inadequate.[123] The key access barriers include lack of workforce capacity; inadequate education, training and infrastructure; and insufficient quality standards and accreditation.[124] Lack of diagnostic capacity and infrastructure leads to misdiagnosis, inadequate antimicrobial treatment, antimicrobial resistance and high mortality.

Even in settings where microbiology laboratory capacity is readily available, the centralised laboratory model (in urban specialised facilities) and traditional microbiological techniques are too slow; results are not available for 24-72 hours. Better, faster diagnostics are needed for the medical urgency of treating life-threatening infections in people with advanced HIV disease, such as bacterial sepsis. Although faster molecular diagnostic techniques are available, their complexity and hefty costs make them unsuitable for adoption and decentralisation in resource-limited settings.[125]

SBI prevention

ART reduces the risk for SBIs; in the START trial, it lowered the incidence of SBIs other than TB among people who started treatment at a CD4 count of >500 cells/mm^3 by 59%,[126] and in the TEMPPRANO trial, SBI incidence decreased by 61% with initiation of ART at a CD4 cell count of >800 cells/mm^3.[127]

Co-trimoxazole reduces hospitalisations, morbidity and mortality among HIV-positive adults, adolescents and children, including those with active TB, and it lowers the risk for malaria, toxoplasmosis, *Pneumocystis* pneumonia, and SBIs.[128,129,130,131,132,133] WHO guidelines have recommended co-trimoxazole prophylaxis since 2006. In 2014, the recommendation was expanded to include lifelong use among all infants, children, adolescents and adults, including pregnant women who are living with HIV, regardless of CD4 cell count in settings where SBIs are highly prevalent.[133]

To prevent TB, people living with HIV take isoniazid with pyridoxine or vitamin B6 (to prevent neuropathy caused by isoniazid) and co-trimoxazole as separate tablets. In December 2016, Cipla received approval from WHOPQ for an FDC of these medicines – called Q-TIB – to reduce the pill burden for people living with HIV, who may already be taking multiple pills daily. Since Cipla has the monopoly on this FDC, it set a price nearly 50% higher for the FDC than the individual products (US$2.75 per patient, per month). In June 2018, Cipla and Unitaid announced a deal to reduce the price to US$1.99 per month,[81] which is still 15% higher than buying the tablets separately.[134] The price reduction is applicable for LMICs, as well as Global Fund and PEPFAR.[81] The price is unlikely to come down further until volumes increase and more suppliers enter the market to generate competition (so far, no other dossier is under evaluation at WHOPQ).[135] Further development of this FDC is required as a paediatric formulation.

Cytomegalovirus (CMV)

In people with advanced HIV disease or AIDS, CMV infection can cause systemic disease; the most common manifestation is CMV retinitis, particularly among people with a CD4 cell count of <100 cells/mm^3. Without treatment, CMV retinitis leads to permanent blindness, and increased mortality, since it is likely to be associated with systemic disease.[136,137] In the pre-ART era, approximately 30% of people with advanced HIV disease or AIDS in high-income countries had CMV retinitis, and it was responsible for over 90% of HIV-related blindness.[138,139] In resource-limited settings where advanced HIV disease or AIDS remain common,

prevalence of CMV retinitis varies regionally,[140] ranging from <5% in Southern Africa to >30% in Southeast Asia, although underreporting is likely, since CMV retinitis often goes undiagnosed.

In resource-limited settings, 21–36% of people with CMV retinitis have already become blind by the time they have an eye exam.[141,142] Despite the prevalence and severe outcomes from CMV retinitis, no interventions are included in the WHO package of care for advanced HIV disease beyond a recommendation to improve access to early diagnosis and affordable treatment.[3]

CMV diagnostics

The gold standard for diagnosing CMV retinitis is a dilated fundoscopic exam of the entire retina.

Since CMV retinitis often occurs among people with low CD4 cell counts who may be poor and may have to travel long distances for care,[143] closer availability of HIV and CMV testing and treatment could improve outcomes. To increase CMV diagnosis and treatment in remote and resource limited settings, MSF's Yangon Project began a 4-day training program in 2006, successfully teaching physicians to diagnose and treat CMV retinitis at the point of care.[144] The project instituted screening of all people with CD4 cell counts of <100 cells/mm^3, CMV symptoms (ocular and extra-ocular), symptoms of meningitis, and disseminated TB – along with routine, CD4-based screenings.[145] Because CMV can cause systemic disease, the virus can be detected in body fluids (blood, saliva or urine) using DNA PCR methods; however, these methods are unavailable in resource-limited settings.

CMV prevention

Because it keeps the immune system healthy, ART is the best prevention for CMV.

CMV treatment

The best treatment for CMV retinitis is oral valganciclovir, since cytomegalovirus is often systemic. The other option is injections of gancyclovir directly into the eye, which are a difficult-to-administer, painful and non-systemic treatment. The high price of valgancyclovir has severely limited access in LMICs, despite a deal between the originator, Roche, and the Medicines Patent Pool to provide valgancyclovir to 138 LMICs at 90% less than the current price, which is 250 CHF per pack (approximately US$250), not including VAT, freight and insurance; the minimum order is 40 packs of 60 tablets.[146]

Diagnostics: a critical component of the package of care

WHO guidelines on advanced HIV disease recommend four key diagnostic tests that are considered essential for implementing a basic package of care: CD4 testing, Xpert MTB/RIF, urinary TB-LAM and CrAg LFA. Despite these tests being included in the WHO Essential Diagnostics List,[147] and although all are commercially available, uptake by national programmes has been slow and limited due to a range of barriers. Table 2 describes the main barriers to implementation.

Table 2: Implementation barriers to OI diagnostics in resource-limited settings

Indication	Test	Facility level	Barriers
Assess immune status	Lab-based CD4	Laboratory	• Scaled-down by countries due to changes in WHO ART initiation guidelines and monitoring recommendations • Delay in relaying patient results • Reliant on efficient sample transport networks • Instrument requires service and maintenance • Low utilisation rate
	POC CD4	Clinic	• Instrument requires power supply, service and maintenance • More expensive than lab-based CD4 testing
TB	Xpert MTB/RIF and Ultra	Laboratory	• Instrument requires power supply, service and maintenance • Limited access and implementation as the initial diagnostic test for TB across countries • GeneXpert instruments are often underutilised • The price (US$10 per cartridge is the 'access price') varies due to distributor mark-ups and other cost drivers • Reliant on sputum samples and invasive non-respiratory samples; not yet validated in other easier-to-collect samples (e.g. urine, whole blood or stool)
	TB-LAM	Clinic	• Unavailability of POC CD4 to identify advanced HIV disease prevents use at the primary healthcare level • Restrictive indication for patients with low CD4 counts based on 2015 evidence • Poor sensitivity in patients with high CD4 counts • Not included in national clinical algorithms • Slow adoption and uptake in national HIV/TB programmes
CM	CrAg LFA	Laboratory Clinic	• Slow implementation of national CrAg screening programmes • Unavailability of POC CD4 to identify advanced HIV disease prevents its use at the primary healthcare level • Low rate of test adoption in national HIV programmes • The need for lumbar punctures to test cerebrospinal fluid may deter use in symptomatic patients • Increased test price due to local distributor's mark-ups

Conclusion and recommendations

Ending deadly and persistent gaps in the global response to AIDS will require changes in both policy and practice, and action at multiple levels. Decisions made in 2018 will have far-reaching effects. We call on policymakers, pharmaceutical corporations, treatment providers, donors, community-based organisations, and all other stakeholders to address the following needs:

1. Timely and appropriate HIV treatment

- Every country should adopt and implement the WHO 'treat all' strategy and ensure that every person living with HIV has access to ARVs.
- Every country should adopt WHO's advanced HIV disease guidelines and provide immunosuppressed patients (those with CD4 <200 cells/mm^3) with the complete package of care for advanced HIV.
- Countries must increase access to viral load testing in ART-experienced patients to allow for a faster switch to alternative regimens for people with resistance.
- Countries should ensure dolutegravir (DTG) is available to all who need it – including women. WHO recommends the consistent use of effective contraception for all women of child-bearing age receiving DTG-based treatment. Countries, HIV programmes and donors must work to improve access to effective contraceptive options for HIV-positive women who do not want to become pregnant, including those who are on, or wish to start, DTG-based treatment.
- ViiV must urgently address access barriers to DTG for infants and children:
    - ViiV should urgently expedite dosing studies for children and the development and registration of a DTG 5 mg dispersible tablet.
    - ViiV should expedite registration of DTG 10 and 25 mg tablets for children in countries where they are needed, including through the WHO Collaborative Registration Procedure and make their registration plans publicly available.
    - Where the product is not yet registered, ViiV should allow countries and organisations to procure and import unregistered DTG using legal options such as import waiver processes.

2. Optimal treatments for opportunistic infections

- Countries should adopt and scale up newer drug combinations for prevention of opportunistic infections, including Q-TIB (a fixed-dose combination treatment of co-trimoxazole, isoniazid and vitamin B6) and 3HP (three months of weekly preventive treatment with rifapentine and isoniazid).
- Countries must improve access to currently available treatments for opportunistic infections by (i) updating guidelines and essential medicines lists and (ii) prioritising registration of appropriate drugs, including through participation in the WHO Collaborative Registration Procedure.
- Manufacturers must ensure Q-TIB and 3HP are registered and affordable. Sanofi should reduce the price of 3HP from the current US$15 per month to allow for scale-up to reach more people living with HIV and develop a fixed-dose combination and a paediatric formulation of 3HP to reduce pill burden.
- Pharmaceutical companies should develop a paediatric formulation Q-TIB.
- Pharmaceutical companies must ensure that oral flucytosine (5-FC), liposomal amphotericin B (L-AMB) and liposomal doxorubicin (PLD) are registered, affordable and widely available in low-resource settings.

Cryptococcal meningitis (CM)

- Countries should align national guidelines with WHO's CM screening, prevention and treatment guidance and implement WHO CM guidance.
- Pharmaceutical companies should develop a sustained-release formulation of 5-FC.

- Mylan should register 5-FC in low- and middle-income countries.
- Gilead should add CM to the indication for procurement of L-AMB at their at-cost price, prioritise registration and ensure availability in low- and middle-income countries.

Kaposi sarcoma (KS)

- WHO should add KS to its advanced HIV disease guidelines.
- WHO should add PLD to the WHO Essential Medicines List.
- Pharmaceutical companies should register PLD broadly and ensure affordable pricing.

3. Better diagnosis of opportunistic infections

Improved access to diagnostic tools is needed to diagnose opportunistic infections and allow early treatment. Key diagnostic tools must be available at all health facilities that receive patients with advanced HIV disease.

- **TB:** National HIV and TB programmes should scale up the use of Xpert MTB/RIF to ensure people living with HIV are diagnosed and treated for TB. TB-LAM should be used routinely in both hospital and ambulatory care settings for all people with HIV who have low CD4 cell counts and TB signs and symptoms.
- **CM:** Countries should routinely use CrAg for all people living with AIDS with CD4 <100 cells/mm^3.
- **Severe bacterial infections:** Governments and other actors should invest in the development of improved diagnostic tools that can rapidly diagnose and distinguish the type of bacterial infection.

Annex 1: ARV Prices in 2018

Low- and middle-income country prices in US$ per person, per year, as quoted by companies. The price in brackets corresponds to the price of one unit (tablet, capsule, mL, etc). Products included in the WHO list of prequalified medicines or approved by the US Food and Drug Administration (as of July 2018) are in bold.

Each originator company applies different eligibility criteria for their ARVs pricing. Thus, countries' eligibilities will vary among companies. Usually, companies create two groups of countries, called 'Category 1' (countries eligible for a lower price) and 'Category 2' (countries offered a higher price). Prices shown here may be ceiling prices; actual prices often vary by LMIC, volumes, and even packaging and labelling requirements.

Paediatric formulations are marked (P). Prices for paediatric products are estimated for the 10 to 10.9 kg weight band based on WHO-recommended dosing. When it was not possible to calculate dosing for the 10 kg weight band, the unit price was used.

ARVs (in alphabetical order)	**Daily dose**	**Originator company**		**Generics companies**						
Abacavir (ABC)		ViiV		Aurobindo	Cipla	Hetero	Micro	Mylan	Strides Shasun	
20 mg/ml oral solution (P)	12 mL	Cat 1 **289 (0.066)**	Cat 2	**274 (0.063)**		**123 (0.028)**				
60 mg dispersible tablet (P)	4				**97 (0.067)**		**127 (0.087)**			
300 mg tablet	2			**139 (0.190)**	**133 (0.182)**	**109 (0.149)**		**113 (0.154)**	**256 (0.350)**	
Atazanavir (ATV)		BMS		Cipla	Emcure	Mylan				
		Cat 1	Cat 2							
150 mg capsule	2	**412 (0.564)**		207 (0.283)	**207 (0.283)**					
200 mg capsule	XX	**(0.677)**			**(0.417)**					
300 mg capsule	1			192 (0.527)	**207 (0.567)**	**183 (0.500)**				
Atazanavir/ritonavir (ATV/r)				Cipla	Emcure	Hetero	Mylan			
300/100 mg tablet	1			**207 (0.567)**	**207 (0.567)**		**183 (0.500)**			
Darunavir (DRV)		Janssen		Aspen	Cipla	Hetero	Mylan			
75 mg tablet (P)	XX	**(0.114)**			**110 (0.150)**					
150 mg tablet (P)	XX	**(0.227)**			**438 (0.300)**					
400 mg tablet	2	**438 (0.600)**		**458 (0.627)**	**608 (0.833)**	**669 (0.917)**	**730 (1.000)**			
600 mg tablet	2	**663 (0.908)**		**658 (0.901)**	**852 (1.167)**	**791 (1.083)**	**913 (1.250)**			
800 mg tablet	1				**1095 (3.000)**					

Continued

ARVs (in alphabetical order)	**Daily dose**	**Originator company**		**Generics companies**								
Dolutegravir (DTG)		ViiV		Aurobindo	Cipla	Hetero						
		Cat 1	Cat 2									
10 mg tablet (P)	XX	**(0.315)**										
25 mg tablet (P)	XX	**(0.585)**										
50 mg tablet	1	**224 (0.612)**	**1764 (4.833)**	**64 (0.174)**	**61 (0.167)**	**61 (0.167)**						
Emtricitabine (FTC)		Gilead		Cipla								
200 mg capsule	1			**49 (0.133)**								
Efavirenz (EFV)		Merck		Aspen	Aurobindo	Cipla	Hetero	Macleods	Micro Labs	Mylan	Strides Shasun	Sun Pharma
		Cat 1	Cat 2									
30 mg/ml suspension (P)	XX	**(0.094)**	**Case-by-case**									
50 mg tablet (P)	XX	**(0.114)**							**(0.054)**	**(0.040)**		
50 mg capsule (P)	XX				**(0.167)**				**(0.060)**			
100 mg tablet (P)	XX									**(0.043)**		
200 mg capsule (P)	3				**127 (0.116)**				**45 (0.041)**			
200 mg tablet (P)	3	**394 (0.360)**	**Case-by-case**						**78 (0.071)**	**62 (0.057)**	**113 (0.103)**	
600 mg tablet	1	**237 (0.650)**		**84 (0.231)**		**40 (0.110)**	**35 (0.095)**	**33 (0.092)**	**34 (0.093)**	**40 (0.108)**	**33 (0.090)**	**37 (0.100)**
Etravirine (ETV)		Janssen		Aspen								
25 mg tablet (P)	XX	**(0.075)**										
100 mg tablet (P)	4	**438 (0.300)**		**438 (0.300)**								
200 mg tablet	2											
Lamivudine (3TC)		ViiV		Aspen	Aurobindo	Cipla	Hetero	Macleods	Micro Labs	Mylan	Strides Shasun	
		Cat 1	Cat 2									
10 mg/ml oral suspension (P)	10 ml	**190 (0.052)**			**46 (0.013)**	**46 (0.013)**	**33 (0.009)**	**38 (0.010)**				
150 mg tablet	2	**114 (0.156)**		**58 (0.080)**	**38 (0.052)**	**28 (0.038)**	**23 (0.032)**	**22 (0.030)**	**24 (0.033)**	**24 (0.033)**	**27 (0.037)**	
300 mg tablet	1					**30 (0.083)**	**26 (0.070)**		**24 (0.067)**			
Lopinavir/ritonavir (LPV/r)		AbbVie		Aurobindo	Cipla	Hetero	Macleods	Mylan				
		Cat 1	Cat 2									
80/20 mg/ml oral solution (P)	4 ml	**150 (0.103)**	**296 (0.203)**									
40/10 mg pellets or granules (P)	XX				**(0.160)**			(0.154)				
100/25 mg tablet (P)	3	**108 (0.099)**	**278 (0.254)**	**141 (0.128)**		**110 (0.100)**	**143 (0.131)**	**91 (0.083)**				
200/50 mg tablet	4	**241 (0.165)**	**740 (0.507)**	**231 (0.158)**	**231 (0.158)**	**237 (0.163)**	**268 (0.183)**	**219 (0.150)**				

Continued

ARVs (in alphabetical order)	**Daily dose**	**Originator company**		**Generics companies**								
Nevirapine (NVP)		Boehringer Ingelheim		Aspen	Aurobindo	Cipla	Hetero	Macleods	Micro Labs	Mylan	Strides Shasun	Sun
10 mg/ml suspension (P)	20 ml				**91 (0.013)**	**91 (0.013)**						
50 mg tablet for oral suspension (P)	4				**61 (0.042)**	**30 (0.021)**						
200 mg tablet	2			63 (0.087)	**34 (0.047)**	**28 (0.038)**	**24 (0.033)**	**27 (0.038)**	**27 (0.037)**	**27 (0.037)**	**27 (0.037)**	**26 (0.035)**
Raltegravir (RAL)		Merck										
		Cat 1	Cat 2									
100 mg powder/sachet (P)	2	**694 (0.95)**										
25 mg tablet (P)	XX	**(0.300)**	**Case-by-case**									
100 mg tablet (P)	XX	**(0.600)**										
400 mg tablet	2	**675 (0.925)**										
Ritonavir (RTV)		AbbVie		Cipla	Mylan							
		Cat 1	Cat 2									
80 mg/ml oral solution (P)	XX	**(0.091)**										
25 mg tablet (P)	XX			**(0.125)**								
50 mg tablet (P)	XX			**(0.250)**								
100 mg tablet	1	**83 (0.114)**			**177 (0.243)**							
Tenofovir (TDF)		Gilead		Aspen	Aurobindo	Cipla	Hetero	Macleods	Mylan	Strides Shasun		
		Cat 1	Cat 2									
Oral powder 40 mg/1g (P)	2	**1290 (1.767)**	**Case-by-case**									
150 mg tablet (P)	XX	**329 (0.900)**										
200 mg tablet	1	**329 (0.900)**										
250 mg tablet	1	**365 (1.00)**										
300 mg tablet	1	**183 (0.500)**		**167 (0.457)**	**84 (0.229)**	**49 (0.133)**	**29 (0.078)**	**30 (0.083)**	**43 (0.117)**	**49 (0.133)**		
Zidovudine (AZT)		ViiV		Aurobindo	Cipla	Hetero	Macleods	Micro Labs	Mylan			
		Cat 1	Cat 2									
10 mg/ml oral solution (P)	24 ml	**416 (0.048)**		**77 (0.009)**	**78 (0.009)**	**78 (0.009)**	**91 (0.010)**					
60 mg tablets (P)	4							**54 (0.037)**				
100 mg capsules	XX			**(0.052)**								
300 mg tablets	2			**76 (0.104)**	**61 (0.083)**	**58 (0.079)**	110 (0.075)	**52 (0.071)**	**68 (0.093)**			

Continued

ARVs (in alphabetical order)	**Daily dose**	**Originator company**		**Generics companies**								
ABC/3TC		ViiV		Aurobindo	Cipla	Hetero	Mylan					
		Cat 1	Cat 2									
60/30 mg tablet (P)	4			**85 (0.058)**	**110 (0.075)**		**80 (0.055)**					
120/60 mg dispersible tablet (P)	2				**94 (0.129)**		**80 (0.110)**					
600/300 mg tablet	1	**275 (0.753)**		**238 (0.653)**	**164 (0.450)**	**121 (0.332)**	**122 (0.333)**					
ABC/3TC/DTG		ViiV		Cipla								
600/300/50 mg tablet	1			207 (0.567)								
TDF/FTC		Gilead		Aspen	Aurobindo	Cipla	Hetero	Macleods	Micro Labs	Mylan	Strides Shasun	Sun
		Cat 1	Cat 2									
300/200 mg tablet	1	**243 (0.667)**	**Case-by-case**	**424 (1.161)**	**56 (0.152)**	**67 (0.183)**	**55 (0.150)**	**49 (0.133)**	**85 0.233)**	**64 (0.175)**	**62 (0.170)**	**53 (0.147)**
TDF/FTC/EFV		Merck		Aspen	Aurobindo	Cipla	Hetero	Macleods	Mylan	Strides Shasun	Sun	
		Cat 1	Cat 2									
300/200/600 mg tablet	1	**613 (1.680)**	**Case-by-case**	251 (0.689)	**157 (0.429)**	**97 (0.267)**	**85 (0.233)**	**79 (0.217)**	**76 (0.208)**	**80 (0.220)**	**85 (0.233)**	
TDF/FTC/DTG				Mylan								
300/200/50 mg tablet	1			79 (0.217)								
TDF/3TC				Aurobindo	Cipla	Hetero	Macleods	Micro Labs	Mylan	Sun Pharma		
300/300 mg tablet	1			**57 (0.155)**	**52 (0.142)**	**43 (0.117)**	**40 (0.108)**	**45 (0.123)**	**50 (0.138)**	**47 (0.128)**		
TDF/3TC/EFV				Aurobindo	Cipla	Hetero	Macleods	Mylan				
300/300/400 mg tablet	1							**75 (0.205)**				
300/300/600 mg tablet	1			**88 (0.240)**	**85 (0.233)**	**79 (0.217)**	**73 (0.200)**	**76 (0.208)**				
TDF/3TC/DTG				Aurobindo	Cipla	Mylan						
300/300/50 mg tablet	1			**85 (0.232)**	85 (0.233)	**75 (0.207)**						
TAF/FTC/DTG				Mylan								
25/200/50 mg tablet	1			**75 (0.207)**								
AZT/3TC		ViiV		Aspen	Aurobindo	Cipla	Hetero	Macleods	Micro Labs	Mylan	Strides Shasun	Sun Pharma
		Cat 1	Cat 2									
60/30 mg tablet (P)	4				**109 (0.075)**	**49 (0.033)**				**46 (0.032)**		
300/150 mg tablet	2	**193 (0.264)**		**145 (0.199)**	**110 (0.150)**	**79 (0.108)**	**67 (0.092)**	**67 (0.092)**	**64 (0.088)**	**64 (0.088)**	**68 (0.093)**	**66 (0.090)**
AZT/3TC/NVP				Cipla	Hetero	Macleods	Mylan	Strides Shasun	Sun Pharma			
60/30/50 mg tablet (P)	4			**92 (0.063)**			**73 (0.050)**	**73 (0.050)**				
300/150/200 mg tablet	2			**91 (0.125)**	**82 (0.113)**	**88 (0.121)**	**79 (0.108)**	**89 (0.122)**	**85 (0.117)**			
AZT/3TC + EFV (co-pack)				Strides Shasun								
300/150 + 600 mg co-pack	1 kit - 3 tabs			**49 (0.133)**								

References

[1] UNAIDS. Fact sheet: Latest global and regional statistics on the status of the AIDS epidemic. [Online]. 2018 Jul [Cited 2018 Jul 19]. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

[2] UNAIDS. AIDS Data 2017. [Online]. 2018 Jul 18 [Cited 2018 Jul 20]. Available from: http://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf

[3] WHO. Guidelines for managing advanced HIV disease and for rapid initiation of antiretroviral therapy. [Online]. 2017 [Cited 2018 Jun 30] Available from: http://apps.who.int/iris/bitstream/handle/10665/255884/9789241550062-eng.pdf;jsessionid=4EB537CF2E352DF9BC4E2B6CE871205A?sequence=1

[4] UNAIDS. AIDS by the numbers. [Online]. 2015 [Cited 2018 Jun 30] Available from: http://www.unaids.org/sites/default/files/media_asset/AIDS_by_the_numbers_2015_en.pdf

[5] UNAIDS Global AIDS update. [Online]. 2016 [Cited 2018 Jun 30] Available from: http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf

[6] Calmy A, Ford N, Meintjes G. The persistent challenge of advanced HIV disease and AIDS in the era of antiretroviral therapy. Clin Infect Dis [Online]. 2018 Mar 4 [Cited 2018 Jul 1];66(Suppl 2). Available from: https://doi.org/10.1093/cid/cix1138

[7] Carmona S, Bor J, Nattey C, et al. Persistent high burden of advanced HIV disease among patients seeking care in South Africa's National HIV Program: data from a nationwide laboratory cohort. Clin Infect Dis [Online]. 2018 Mar 4 [Cited 2018 Jun 30];66(Suppl 2). Available from: https://doi.org/10.1093/cid/ciy045

[8] IeDEA and COHERE Cohort Collaborations. Global trends in CD4 cell count at the start of antiretroviral therapy: collaborative study of treatment programs. Clin Infect Dis [Online]. 2018 Mar 5 [Cited 2018 Jun 30];66(6). Available from: https://doi.org/10.1093/cid/cix915

[9] Egger M, May M, Chêne G, et al; ART Cohort Collaboration. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet [Online]. 2002 Jul 13 [Cited 2018 Jul 1];360(9327). Available from: https://doi.org/10.1016/S0140-6736(02)09411-4

[10] Manosuthi W, Chaovavanich A, Tansuphaswadikul S, et al. Incidence and risk factors of major opportunistic infections after initiation of antiretroviral therapy among advanced HIV-infected patients in a resource-limited setting. J Infect [Online]. 2007 Nov [Cited 2018 Jul 1];55(5). Available from: https://doi.org/10.1016/j.jinf.2007.07.002

[11] Siika A, McCabe L, Bwakura-Dangarembizi M, et al; REALITY Trial Team. Late presentation with HIV in Africa: phenotypes, risk, and risk stratification in the REALITY trial. Clin Infect Dis [Online]. 2018 Mar 4 [Cited 2018 Jul 1];66(Suppl 2). Available from: https://doi.org/10.1093/cid/cix1142

[12] Boulle A, Bock P, Osler M, et al. Antiretroviral therapy and early mortality in South Africa. Bulletin of the World Health Organization [Online]. 2008 Sep [Cited 2018 Jul 7];86(9). Available from: http://www.who.int/bulletin/volumes/86/9/07-045294/en/86:9

[13] Osler M, Hilderbrand K, Goemaere E, et al. The continuing burden of advanced HIV disease over 10 years of increasing antiretroviral therapy coverage in South Africa. Clin Infect Dis [Online]. 2018 Mar 4 [Cited 2018 Jul 7];66(Suppl 2). Available from: https://doi.org/10.1093/cid/cix1140

[14] Ousley J, Niyibizi AA, Wanjala S, et al. High proportions of patients with advanced HIV are antiretroviral therapy experienced: hospitalization outcomes from 2 sub-Saharan African sites. Clin Infect Dis [Online]. 2018 Mar 4 [Cited 2018 Jul 7];66(Suppl 2). Available from: https://doi.org/10.1093/cid/ciy103

[15] MSF. Out of focus: how millions of people in west and central Africa are being left out of the global AIDS response. [Online]. 2016 Apr [Cited 2018 Jun 30]. Available from: https://www.msf.org/sites/msf.org/files/2016_04_hiv_report_eng.pdf

[16] UNAIDS. Miles to go: Global AIDS update 2018. [Online]. 2018 Jul [Cited 2018 Jul 20]. Available from: http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf

[17] Ford N, Meintjes G, Vitoria M, Greene G, Chiller, T. The evolving role of CD4 cell counts in HIV care. Curr Opin HIV AIDS [Online]. 2017 Mar [Cited 2018 Jul 5];12(2). Available from: https://doi.org/10.1097/COH.0000000000000348

[18] Peeling RW, Ford N. Reprising the role of CD4 cell count in HIV programmes. Lancet HIV [Online]. 2017 Sep [Cited 2018 Jul 5];4(9). Available from: https://doi.org/10.1016/S2352-3018(17)30096-6

[19] Indravudh PP, Choko AT, Corbett EL. Scaling up HIV self-testing in sub-Saharan Africa: a review of technology, policy and evidence. Curr Opin Infect Dis [Online]. 2018 Feb [Cited 2018 Jul 5];31(1). Available from: https://doi.org/10.1097/QCO.0000000000000426

[20] Omega Diagnostics Group PLC. Omega Diagnostics and Burnet Institute announce VISITECT® CD4 CE-Marking. [Online]. 2017 Dec 1 [Cited 2018 Jul 5]. Available from: http://www.omegadiagnostics.com/News-Events/Omega-News/entryid/71

[21] Peeling RW, Holmes KK, Mabey D, Ronald A. Rapid tests for sexually transmitted infections (STIs): the way forward. Sex Transm Infect [Online]. 2006 Dec [Cited 2018 Jul 3];82(Suppl 5). Available from: http://doi.org/10.1136/sti.2006.024265

[22] WHO. HIV drug resistance report 2017. [Online]. 2017 [Cited 2018 Jul 1] Available from: http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf?sequence=1

[23] Vitoria M, Hill A, Ford N, et al. The transition to dolutegravir and other new antiretrovirals in low- and middle-income countries - what are the issues? AIDS [Online]. 2018 May 9 [Cited 2018 Jul 2]. Available from: http://doi.org/10.1097/QAD.0000000000001845

[24] Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. Lancet Infect Dis [Online]. 2018 Mar [Cited 2018 Jun 30];18(3). Available from: http://doi.org/10.1016/S1473-3099(17)30702-8

[25] Walmsley SL, Antela A, Clumeck N, et al; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med [Online]. 2013 Nov 7 [Cited 2018 Jul 9];369(19). Available from: http://doi.org/10.1056/NEJMoa1215541

[26] Kanters S, Vitoria M, Doherty M, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV [Online]. 2016 Nov [Cited 2018 Jul 1];3(11). Available from: https://doi.org/10.1016/S2352-3018(16)30091-1

[27] Clinton Health Access Initiative. ARV market report. [Online]. 2017 Sep [Cited 2018 Jul 2]. Available from: https://clintonhealthaccess.org/content/uploads/2017/09/2017-ARV-Market-Report_Final.pdf

[28] UNAIDS. New high-quality antiretroviral therapy to be launched in South Africa, Kenya and over 90 low- and middle-income countries at reduced price. Press release. [Online]. 2017 Sep 21 [Cited 2018 Jul 2]. Available from: http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2017/september/20170921_TLD

[29] WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Policy Brief. [Online]. 2015 Nov [Cited 2018 Jul 2]. Available from: http://apps.who.int/iris/bitstream/handle/10665/198064/9789241509893_eng.pdf?sequence=1

[30] Dooley K, Kaplan R, Mwelase N, et al. Safety and efficacy of dolutegravir-based ART in TB/HIV coinfected adults at week 24. Abstract 33. Conference on Retroviruses and Opportunistic Infections; Boston, Massachusetts, United States. [Online]. 2018 Mar 4-7 [Cited 2018 Jul 3]. Available from: http://www.croiconference.org/sessions/safety-and-efficacy-dolutegravir-based-art-tbhiv-coinfected-adults-week-24

[31] WHO. Policy brief: Update on antiretroviral regiments for treating and preventing HIV infection and update on early infant diagnosis of HIV. 2018 Jul 23.

[32] Lancet. Dolutegravir for HIV: a lesson in pregnancy safety research. Lancet [Online] 2018 Jun 9 [Cited 2018 Jul 1];391(10137). Available from: https://doi.org/10.1016/S0140-6736(18)31265-0

[33] Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health [Online]. 2018 Jul [Cited 2018 Jul 2];6(7). Available from: https://doi.org/10.1016/S2214-109X(18)30218-3

[34] HIV i-Base. DTG alert, PK reports and more. HIV treatment bulletin [Online]. 2018 Jun 8 [Cited 2018 Jul 2];19(10). Available from: http://i-base.info/htb-issue-10-online-08-june-2018-dtg-alert-pk-reports-and-more/

[35] Brent RL. Utilization of animal studies to determine the effects and human risks of environmental toxicants (Drugs, Chemicals, and Physical Agents). Pediatrics [Online]. 2004 Apr [Cited 2016 Jul 4];113(Suppl 3). Available from: http://pediatrics.aappublications.org/content/113/Supplement_3/984.long

[36] HIV i-Base. ViiV Dear Doctor letter: Neural tube defects reported in infants born to women exposed to dolutegravir at the time of conception. [Online]. 2018 Jun 8 [Cited 2018 Jul 2]. Available from: http://i-base.info/htb/34302

[37] WHO. Statement on DTG: Potential safety issue affecting women living with HIV using dolutegravir at the time of conception. [Online]. 2018 May 18 [Cited 2018 Jul 1]. Available from: http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf

[38] United Nations Population Fund. World population dashboard: family planning. [Online]. [Cited 2018 Jul 2]. Available from: https://www.unfpa.org/data/world-population-dashboard

[39] WHO. List of prequalified medicines. [Online]. [Cited 2018 Jul 2]. Available from: https://extranet.who.int/prequal/content/prequalified-lists/medicines

[40] Clinton Health Access Initiative. ARV market report. [Online]. 2017 Sep [Cited 2018 Jul 2]. Available from: https://clintonhealthaccess.org/content/uploads/2017/09/2017-ARV-Market-Report_Final.pdf

[41] UNAIDS. New high-quality antiretroviral therapy to be launched in South Africa, Kenya and over 90 low- and middle-income countries at reduced price. Press release. [Online]. 2017 Sep 21 [Cited 2018 Jul 2]. Available from: http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2017/september/20170921_TLD

[42]'t Hoen, E. Dolutegravir patent licences can provide access to all. Medicines Law and Policy [Online]. 2017 Jul 26 [Cited 2018 Jul 7]. Available from: https://medicineslawandpolicy.org/2017/07/dolutegravir-patent-licences-smoke-screen-or-breath-of-fresh-air/

[43] The Global Fund. Price and quality reporting. [Online]. [Cited 2018 Jul 7]. Available from: https://www.theglobalfund.org/en/sourcing-management/price-quality-reporting/

[44] WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. [Online]. 2013 Jun [Cited 2018 Jul 2]. Available from: http://apps.who.int/iris/bitstream/handle/10665/85321/9789241505727_eng.pdf;jsessionid=7A0D37E671CF0C573B67A939DAAA68D0?sequence=1

[45] WHO. AIDS Medicines and Diagnostics Meeting presentation. 2018 Apr.

[46] Medicines Patent Pool. Medicines Patent Pool, ViiV Healthcare collaborate to treat paediatric HIV. Press release. [Online]. 2013 Feb 27 [Cited 2018 Jul 2] Available from: https://medicinespatentpool.org/mpp-media-post/medicines-patent-pool-viiv-healthcare-collaborate-to-treat-paediatric-hiv/

[47] MSF. MSF urges ViiV to register its paediatric HIV drug formulation of dolutegravir broadly across low and middle income countries. Letter. [Online]. 2017 Dec 1 [Cited 2018 Jul 3]. Available from: https://msfaccess.org/sites/default/files/2018-04/HIV_Viiv%20DTG%20Peds%20Letter%20-%20World%20AIDS%20Day%202017.pdf

[48] WHO. PADO 3 Review: Developing implementation considerations and informing future directions. [Online]. 2018 Feb 5 [Cited 2018 Jul 2]. Available from: https://iasociety.org/Web/WebContent/File/ILF__Report_back__PADO_3_review__Penazzato.pdf

[49] Paediatric Action Plan. Individual Commitments. Paediatric HIV: Rome Action Plan follow-up. [Online]. 2017 Nov [Cited 2018 Jul 2]. Available from: https://www.paediatrichivactionplan.org/viivhealthcare-b

[50] Unitaid. New partnership to help fast-track affordable HIV medicine for children living with HIV. [Online]. 2018 Jul 19 [Cited 2018 Jul 20]. Available from: https://unitaid.org/news-blog/new-partnership-to-help-fast-track-affordable-hiv-medicine-for-children-living-with-hiv/#en

[51] WHO. Global TB report 2017. [Online]. 2017 [Cited 2018 Jul 2]. Available from: http://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf

[52] CDC. Latent TB infection: a guide for primary health care providers. [Online]. 2013 [Cited 2018 Jul 2]. Available from: https://www.cdc.gov/tb/publications/ltbi/pdf/targetedltbi.pdf

[53] WHO. Guidelines for treatment of tuberculosis. 4th ed. [Online]. 2010 [Cited 2018 Jul 3]. Available from: http://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf?sequence=1

[54] WHO. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB. [Online]. 2010 Dec 6 [Cited 2018 Jul 3] Available from: http://www.who.int/tb/laboratory/roadmap_xpert_mtb-rif.pdf

[55] WHO. Next-generation Xpert® MTB/RIF Ultra assay recommended by WHO. [Online]. 2017 Mar 24 [Cited 2018 Jul 3]. Available from: http://www.who.int/tb/features_archive/Xpert-Ultra/en/

[56] MSF. Out of step 2017. [Online]. 2017 [Cited 2018 Jul 2]. Available from: https://msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_Report_OutOfStep_3rdEd_ENG_2017.pdf

[57] Ardizzoni E, Fajardo E, Saranchuk P, et al. Implementing the Xpert® MTB/RIF diagnostic test for tuberculosis and rifampicin resistance: outcomes and lessons learned in 18 countries. PLoS One [Online]. 2015 Dec 15 [Cited 2018 Jul 3];10(12). Available from: https://doi.org/10.1371/journal.pone.0144656

[58] Lawn SD, Nicol MP. Xpert® MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. Future Microbiol [Online]. 2011 Sep [Cited 2018 Jul 2];6(9). Available from: https://doi.org/10.2217/fmb.11.84

[59] Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet. [Online] 2007 Jun 16 [Cited 2016 Dec 28];369(9578). Available from: https://www.ncbi.nlm.nih.gov/pubmed/17574096

[60] Gupta RK, Lawn SD, Bekker L-G, et al. Impact of human immunodeficiency virus and CD4 count on tuberculosis diagnosis: analysis of city-wide data from Cape Town, South Africa. Int J Tuberc Lung Dis [Online]. 2013 Aug [Cited 2018 Jul 3];17(8). Available from: https://doi.org/10.5588/ijtld.13.0032

[61] Lawn SD, Kerkhoff AD, Burton R, et al. Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort. BMC Med [Online]. 2017 Mar 21 [Cited 2018 Jul 2];15(1). Available from: https://doi.org/10.1186/s12916-017-0822-8

[62] WHO. The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: Policy Update. [Online]. 2015 [Cited 2018 Jul 2]. Available from: http://www.who.int/tb/publications/use-of-lf-lam-tb-hiv/en/

[63] Peter JG, Zijenah LS, Chanda D, et al. Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. Lancet [Online]. 2016 Mar 19 [Cited 2018 Jul 9];387(10024). Available from: https://doi.org/10.1016/S0140-6736(15)01092-2

[64] Gupta-Wright A, Corbett AL, van Oosterhout JJ, et al. Urine-based screening for tuberculosis: a randomized trial in HIV-positive inpatients. Abstract 38LB. Conference on Retroviruses and Opportunistic Infections; Boston, Massachusetts, United States. [Online]. 2018 Mar 4-7. [Cited 2018 Jul 9]. Available from: http://www.croiconference.org/sessions/urine-based-screening-tuberculosis-randomized-trial-hiv-positive-inpatients

[65] Huerga H, Ferlazzo G, Bevilacqua P, et al. Incremental yield of including Determine-TB LAM assay in diagnostic algorithms for hospitalized and ambulatory HIV-positive patients in Kenya. PLoS One [Online]. 2017 Jan 26 [Cited 2018 Jul 7];12(1). Available from: https://doi.org/10.1371/journal.pone.0170976

[66] Kerkhoff AD, Barr DA, Schutz C, et al. Disseminated tuberculosis among hospitalised HIV patients in South Africa: a common condition that can be rapidly diagnosed using urine-based assays. Scientific Reports [Online]. 2017 Sep 7 [Cited 2018 Jul 7];7. Available from: https://doi.org/10.1038/s41598-017-09895-7

[67] Suwanpimolkul G, Kawkitinarong K, Manosuthi W, et al. Utility of urine lipoarabinomannan (LAM) in diagnosing tuberculosis and predicting mortality with and without HIV: prospective TB cohort from the Thailand Big City TB Research Network. Int Jour Inf Dis [Online]. 2017 Jun [Cited 2018 Jul 7];59. Available from: https://doi.org/10.1016/j.ijid.2017.04.017

[68] Floridia M, Ciccacci F, Andreotti M, et al. Tuberculosis case finding with combined rapid point-of-care assays (Xpert MTB/RIF and Determine TB LAM) in HIV-positive individuals starting antiretroviral therapy in Mozambique. Clin Inf Dis [Online]. 2017 Nov 13 [Cited 2018 Jul 7];65(11). Available from: https://doi.org/10.1093/cid/cix641

[69] Sabur NF, Esmail A, Brar MS, Dheda K. Diagnosing tuberculosis in hospitalized HIV-infected individuals who cannot produce sputum: is urine lipoarabinomannan testing the answer? BMC Inf Dis [Online]. 2017 Dec 28 [Cited 2018 Jul 7];17(1). Available from: https://doi.org/10.1186/s12879-017-2914-7

[70] Lawn SD, Kerkhoff AD, Burton R, et al. Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort. BMC Med [Online]. 2017 Mar 21 [Cited 2018 Jul 7];15(1). Available from: https://doi.org/10.1186/s12916-017-0822-8

[71] Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. Plos Med [Online]. 2012 [Cited 2018 Jul 3]. Available from: https://doi.org/10.1371/journal.pmed.1001270

[72] Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med [Online]. 2012 Jul 24 [Cited 2018 Jul 7];9(7). Available from: https://doi.org/10.1371/journal.pmed.1001270

[73] Godfrey-Faussett, P. Policy statement on preventive therapy against tuberculosis in people living with HIV: Report of a meeting held in Geneva 18-20 February 1998. WHO and UNAIDS [Online]. 1998 [Cited 2018 Jul 3]. Available from: http://apps.who.int/iris/bitstream/handle/10665/64509/WHO_TB_98.255.pdf?sequence=1

[74] Ayele HT, van Mourik MS, Debray TP, Bonten MJ. Isoniazid prophylactic therapy for the prevention of tuberculosis in HIV infected adults: a systematic review and meta-analysis of randomized trials. PLoS One [Online]. 2015 Nov 9 [Cited 2018 Jul 3];10(11). Available from: https://doi.org/10.1371/journal.pone.0142290

[75] WHO. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. [Online]. 2018 [Cited 2018 Jul 3]. Available from: http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf?sequence=1

[76] Stennis NL, Burzynski JN, Herbert C, Nilsen D, Macaraig M. Treatment for tuberculosis infection with 3 months of isoniazid and rifapentine in New York City Health Department clinics. Clin Infect Dis [Online]. 2016 Jan 1 [Cited 2018 Jul 3];62(1). Available from: https://doi.org/10.1093/cid/civ766

[77] Stop TB Partnership. GDF products list. [Online]. 2018 [Cited 2018 Jul 3]. Available from: http://www.stoptb.org/gdf/drugsupply/drugs_available.asp

[78] Sanofi. Priftin: Highlights of prescribing information. [Online]. Revised 2017 Aug [Cited 2018 Jul 3]. Available from: http://products.sanofi.us/priftin/priftin.pdf

[79] Brooks KM, Pau AK, George JM, et al. Early termination of a PK study between dolutegravir and weekly isoniazid/rifapentine. Abstract 409a. Conference on Retroviruses and Opportunistic Infections; Seattle, Washington, United States. [Online]. 2017 Feb 13-16 [Cited 2018 Jul 7]. Available from: http://www.croiconference.org/sessions/early-termination-pk-study-between-dolutegravir-and-weekly-isoniazidrifapentine

[80] Swindells S, Ramchandani R, Gupta A. et al. One Month of Rifapentine/Isoniazid to prevent TB in People with HIV: BRIEF-TB/A5279. Abstract 37-LB. Conference on Retroviruses and Opportunistic Infections; Boston, Massachusetts, United States. [Online]. 2018 Mar 4-7 [Cited 2018 Jul 3]. Available from: http://www.croiconference.org/sessions/one-month-rifapentineisoniazid-prevent-tb-people-hiv-brief-tba5279

[81] Unitaid. Price cut on medicine will help preserve the health of more people living with HIV. Press release. [Online]. 2018 June 8 [Cited 2018 Jul 3]. Available from: https://unitaid.eu/news-blog/price-cut-on-medicine-will-help-preserve-the-health-of-more-people-living-with-hiv/#en

[82] Brust JCM, Shah NS, Mlisana K et al. Improved survival and cure rates with concurrent treatment for multidrug-resistant tuberculosis-human immunodeficiency virus coinfection in South Africa. Clin Infect Dis [Online]. 2018 Apr 3 [Cited 2018 Jul 7];66(8). Available from: https://doi.org/10.1093/cid/cix1125

[83] Conradie F, Diacon AH, Everitt D, et al. The NIX-TB Trial of pretomanid, bedaquiline and linezolid to treat XDR-TB. Abstract 80-LB. Conference on Retroviruses and Opportunistic Infections; Seattle, Washington, United States. [Online]. 2017 Feb 13-16 [Cited 2018 Jul 7]. Available from: http://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb

[84] Ferlazzo G, Mohr E, Laxmeshwar C, et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. Lancet Infect Dis [Online]. 2018 May [Cited 2018 Jul 8];18(5). Available from: https://doi.org/10.1016/S1473-3099(18)30100-2

[85] Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis [Online]. 2017 May 5 [Cited 2018 Jul 4]; 17(8). Available from http://doi.org/10.1016/S1473-3099(17)30243-8.

[86] WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. [Online]. 2018 Mar [Cited 2018 Jul 4]. Available from: http://apps.who.int/iris/bitstream/handle/10665/260399/9789241550277-eng.pdf;jsessionid=E8E0AD0974D6871DC14C91AE471E06E5?sequence=1

[87] Immuno-Mycologics Inc. CrAg LFA. [Online]. [Cited 2018 Jul 4]. Available from: http://www.immy.com/products/lateral-flow-assays/crag-lfa/

[88] WHO. Rapid Advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. [Online]. 2011 [Cited 2018 Jul 4]. Available from: http://apps.who.int/iris/bitstream/handle/10665/44786/9789241502979_eng.pdf?sequence=1

[89] Greene G, Vallabhaneni S, Chung JH, Chiller T. Cryptococcal antigen screening and treatment: the current state of global screening programs to prevent death from cryptococcal infection. Curr Fungal Infect Rep [Online]. 2015 Dec [Cited 2018 Jul 4];9(4). Available from: https://doi.org/10.1007/s12281-015-0246-x

[90] Biosynex SA, France. BioSynex CryptoPS. [Online]. [Cited 2018 Jul 4] Available from: https://www.biosynex.com/flyers/pro/mycologie/cryptops.pdf

[91] Mpoza E, Mukaremera L, Kundura DA, et al. Evaluation of a point-of-care immunoassay test kit "StrongStep" for cryptococcal antigen detection. PLoS One [Online]. 2018 Jan 5 [Cited 2018 Jul 4];13(1)e0190652. Available from: https://doi.org/10.1371/journal.pone.0190652

[92] ERA Biology. Catalog. [Online]. [Cited 2018 Jul 4] Available from: http://www.era-bio.com/ueditor/php/upload/file/20170517/Catalogue-2017.PDF

[93] Temfack E, Kouanfack C, Mossiang L, et al. Cryptococcal antigen screening in asymptomatic HIV-infected antiretroviral naïve patients in Cameroon and evaluation of the new semi-quantitative Biosynex CryptoPS Test. Front Microbiol [Online]. 2018 Mar 13 [Cited 2018 Jul 4];9. Available from: https://doi.org/10.3389/fmicb.2018.00409

[94] Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. N Engl J Med [Online]. 2018 Mar 15 [Cited 2018 Jul 5];378(11). Available from: https://doi.org/10.1056/NEJMoa1710922

[95] Oladele Ro, Otu AA, Richardson MD, Denning, DW. Diagnosis and management of pneumocystis pneumonia in resource-poor settings. J Health Care Poor Underserved [Online]. 2018 [Cited 2018 Jul 6];29(1). Available from: https://doi.org/10.1353/hpu.2018.0010

[96] Lowe DM, Rangaka MX, Gordon F, James CD, Miller RF. Pneumocystis jirovecii pneumonia in tropical and low and middle income countries: a systematic review and meta-regression. PloS One [Online]. 2013 Aug 2 [Cited 2018 Jul 6];8(8)e0069969. Available from: https://doi.org/10.1371/journal.pone.0069969

[97] Merry M, Boulaware DR. Cryptococcal meningitis treatment strategies affected by the explosive cost of flucytosine in the United States: a cost-effectiveness analysis. Clin Infect Dis [Online]. 2016 Mar 23 [Cited 2018 Jul 4]:62(12). Available from: https://doi.org/10.1093/cid/ciw151

[98] Mylan Laboratories. Mylan expands access to HIV/AIDS medicines with launch of first generic Sustiva® tablets. Press release. [Online]. 2018 Feb 1 [Cited 2018 Jul 4]. Available from: http://newsroom.mylan.com/2018-02-01-Mylan-Expands-Access-to-HIV-AIDS-Medicines-with-Launch-of-First-Generic-Sustiva-R-Tablets

[99] Vidal. Consumer reference for medical information. [Online]. 2018 May 22 [Cited 2018 Jul 4]. Available from: https://eurekasante.vidal.fr/medicaments/vidal-famille/medicament-dancot01-ANCOTIL.html

[100] Mylan. Mylan completes acquisition of Meda. Press release. [Online]. 2016 Aug 5 [Cited 2018 Jul 4]. Available from: http://newsroom.mylan.com/2016-08-05-Mylan-Completes-Acquisition-of-Meda

[101] WHO. First flucytosine prequalified. News. [Online]. 2018 Mar 14 [Cited 2018 Jul 4]. Available from: https://extranet.who.int/prequal/news/first-flucytosine-prequalified

[102] Medicine Price Registry. What should your medicines cost? [Online]. 2018 May 27 [Cited 2104 Jul 3]. Available from: https://mpr.code4sa.org/#search:Amphotericin%20b

[103] MSF. Letter to Gilead Sciences requesting expansion of not-for-profit price of key drug L-AMB. [Online]. 2017 Feb 16 [Cited 2018 Jul 4]. Available from: https://msfaccess.org/sites/default/files/MSF_assets/Access/Docs/Access_Letter_L-AMB%20for%20CryptoMeningitisGilead_ENG_2017.pdf

[104] Jarvis JN, Leeme TB, Chofle AA, et al. AMBITION-CM: High-dose liposomal amphotericin for HIV-related cryptococcal meningitis. Abstract 82. Conference on Retroviruses and Opportunistic Infections; Seattle, Washington, United States. [Online]. 2017 Feb 13-16 [Cited 2018 Jul 4]. Available from: http://www.croiconference.org/sessions/ambition-cm-high-dose-liposomal-amphotericin-hiv-related-cryptococcal-meningitis

[105] Cheng W, Wu Y, Wen Y, et al. Cotrimoxazole prophylaxis and antiretroviral therapy: an observational cohort study in China. Bull World Health Organ [Online]. 2015 Mar 1 [Cited 2018 Jul 6];93(3). Available from: https://doi.org/10.2471/BLT.14.142745

[106] Date AA, Vitoria M, Granich R, Banda M, Fox MY, Gilks C. Implementation of co-trimoxazole prophylaxis and isoniazid preventive therapy for people living with HIV. Bull World Health Organ [Online]. 2009 Oct 23 [Cited 2018 Jul 6];88(4). Available from: https://doi.org/10.2471/BLT.09.066522

[107] Suthar AB, Granich R, Mermin J, Van Rie A. Effect of cotrimoxazole on mortality in HIV-infected adults on antiretroviral therapy: a systematic review and meta- analysis. Bull World Health Organ [Online]. 2012 Feb 1 [Cited 2018 Jul 6];90(2). Available from: https://doi.org/10.2471/BLT.11.093260

[108] Bardfield J, Agins B, Palumbo M, Wei AL, Morris J, Marston B. Improving rates of cotrimoxazole prophylaxis in resource-limited settings: implementation of a quality improvement approach. Int J Qual Health Care [Online]. 2014 Dec 1 [Cited 2018 Jul 6];26(6). Available from: https://doi.org/10.1093/intqhc/mzu085

[109] Chang HM, Tsai HC, Lee SS, et al. High daily doses of trimethoprim/sulfamethoxazole are an independent risk factor for adverse reactions in patients with pneumocystis pneumonia and AIDS. J Chin Med Assoc [Online]. 2016 Jun [Cited 2018 Jul 8];79(6). Available from: https://doi.org/10.1016/j.jcma.2016.01.007

[110] Dubrow R, Qin L, Lin H, et al. Association of CD4+ T-cell count, HIV-1 RNA viral load, and antiretroviral therapy with Kaposi sarcoma risk among HIV-infected persons in the United States and Canada. J Acquir Immune Defic Syndr [Online]. 2017 Aug [Cited 2018 Jul 4 ;75(4). Available from: https://doi.org/10.1097/QAI.0000000000001394

[111] El-Mallawany NK, McAtee CL, Campbell LR, Kazembe PN. Pediatric Kaposi sarcoma in context of the HIV epidemic in sub-Saharan Africa: current perspectives. Pediatric Health Med Ther [Online]. 2018 Apr 19 [Cited 2018 Jul 4];9. Available from: https://doi.org/10.2147/PHMT.S142816

[112] Nasti G, Talamini R, Antinori A, et al; AIDS clinical trial group staging system in the HAART era--the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive from Antiretrovirals. AIDS-related Kaposi's Sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the HAART era--the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive From Antiretrovirals. J Clin Oncol [Online]. 2003 Aug 1 [Cited 2018 Jul 4];21(15). Available from: https://doi.org/10.1200/JCO.2003.10.162

[113] WHO. Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults. [Online]. 2014 [Cited 2018 Jul 4] Available from: http://apps.who.int/iris/bitstream/handle/10665/136863/9789241548915_eng.pdf?sequence=1

[114] Cheng CH, Hsu YH. Immune reconstitution inflammatory syndrome-associated disseminated Kaposi's sarcoma in a patient infected with human immunodeficiency virus: Report of an autopsy case. Tzu-chi medical journal [Online]. 2017 [Cited 2018 Jul 4];29(1). Available from: https://doi.org/10.4103/tcmj.tcmj_9_17

[115] Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. AIDS [Online]. 2013 Jun 19 [Cited 2018 Jul 4];27(10). Available from: https://doi.org/10.1097/QAD.0b013e328360a5a1

[116] Northfelt DW, Dezube BJ, Thommes JA, et al. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. J Clin Oncol [Online]. 1998 Jul [Cited 2018 Jul 4];16(7). Available from: https://doi.org/10.1200/JCO.1998.16.7.2445

[117] Stewart S, Jablonowski H, Goebel FD, et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol [Online]. 1998 Feb [Cited 2018 Jul 4];16(2). Available from: https://doi.org/10.1200/JCO.1998.16.2.683

[118] Fardhdiani V, Molfino L, Zamudio AG, et al. HIV- associated Kaposi's sarcoma in Maputo, Mozambique: outcomes in a specialized treatment center, 2010-2015. Infect Agent Cancer [Online]. 2018 Jan 19 [Cited 2018 Jul 4];13(5). Available from: https://doi.org/10.1186/s13027-018-0177-6

[119] Coldiron M, Gutierrez Zamudio AG, Sebastiani T, et al. Pegylated liposomal doxorubicin for the treatment of Kaposi's sarcoma in Maputo, Mozambique: first results of a prospective study. Presentation. Médecins Sans Frontières UK Scientific Days: Medical Research 2017. [Online]. 2018 May 5 [Cited 2018 Jul 11]. Available from: https://f1000research.com/slides/6-721

[120] Royal Pharmaceutical Society. Medicines Complete. Doxorubicin hydrochloride monograph, British National Formulary. [Online]. [Cited 2018 Jul 10]. Available from: https://doi.org/10.18578/BNF.938546664

[121] Gaskell KM, Feasey NA, Heyderman RS. Management of severe non-TB bacterial infection in HIV-infected adults. Expert Rev Anti Infect Ther [Online]. 2015 [Cited 2018 Jul 5];13(2). Available from: https://doi.org/10.1586/14787210.2015.995631

[122] Ford N, Shubber Z, Meintjes G, et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. Lancet HIV [Online]. 2015 [Cited 2018 Jul 3];2(10):e438-44. Available from: https://doi.org/10.1016/S2352-3018(15)00137-X

[123] Ombelet S, Ronat JB, Walsh T, et al. Clinical bacteriology in low-resource settings: today's solutions. Lancet Infect Dis [Online]. 2018 Mar 5 [Cited 2018 Jul 5]. Available from: https://doi.org/10.1016/S1473-3099(18)30093-8

[124] Wilson ML, Fleming KA, Kuti MA, Looi LM, Lago N, Ru K. Access to pathology and laboratory medicine services: a crucial gap. Lancet [Online]. 2018 May 12 [Cited 2018 Jul 5];391(10133). Available from: https://doi.org/10.1016/S0140-6736(18)30458-6

[125] Sinha M, Jupe J, Mack H, Coleman TP, Lawrence SM, Fraley SI. Emerging technologies for molecular diagnosis of sepsis. Clin Microbiol Rev [Online]. 2018 Feb 28 [Cited 2018 Jul 5];31(2). Available from: https://doi.org/10.1128/CMR.00089-17

[126] O'Connor, J, Vjecha, MJ, Phillips, AN et al; INSIGHT START study group. Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with a CD4 cell count of more than 500 cells per µL: secondary outcome results from a randomised controlled trial. Lancet HIV [Online]. 2017 [Cited 2018 Jul 5]. Available from: http://doi.org/10.1016/S2352-3018(16)30216-8

[127] TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive Therapy in Africa. N Engl J Med [Online]. 2015 Aug 27 [Cited 2018 Jul 5];373(9). Available from: http://doi.org/10.1056/NEJMoa1507198

[128] Anglaret X, Chêne G, Attia A, et al; Cotrimo-CI Study Group. Early chemoprophylaxis with trimethoprim- sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. Lancet [Online]. 1999 May 1 [Cited 2018 Jul 5];353(9163). Available from: https://doi.org/10.1016/S0140-6736(98)07399-1

[129]Mermin J, Lule J, Ekwaru JP, et al. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. Lancet [Online]. 2004 Oct 16 [Cited 2018 Jul 5];364(9443). Available from: https://doi.org/10.1016/S0140-6736(04)17225-5

[130] Mermin J, Ekwaru JP, Liechty CA, et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. Lancet [Online]. 2006 Apr 15 [Cited 2018 Jul 5];367(9518). Available from: https://doi.org/10.1016/S0140-6736(06)68541-3

[131] Suthar AB, Vitoria MA, Nagata JM, et al. Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. Lancet HIV [Online]. 2015 Apr [Cited 2018 Jul 4];2(4):e137-50. Available from: https://doi.org/10.1016/S2352-3018(15)00005-3

[132] Walker AS, Ford D, Gilks CF, et al. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. Lancet [Online]. 2010 Mar 29 [Cited 2018 Jul 5]375(9722). Available from: https://doi.org/10.1016/S0140-6736(10)60057-8

[133] WHO. Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxozole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach. December 2014 Supplement to the 2013 Consolidated Guidelines on use of Antiretroviral Drugs for Treating and Preventing HIV. [Online]. 2014 Dec [Cited 2018 Jul 5]. Available from: http://apps.who.int/iris/bitstream/handle/10665/145719/9789241508193_eng.pdf?sequence=1

[134] Ravelo JL. Deal slashes drug price of 3 in 1 pill for people living with HIV. Devex [Online]. 2018 Jun 8 [Cited 2018 Jul 5]. Available from: https://www.devex.com/news/deal-slashes-drug-price-of-3-in-1-pill-for-people-living-with-hiv-92910?utm_source=English+list&utm_campaign=9bfb4ab402-News%2FRecap+June+2018_COPY_02&utm_medium=email&utm_term=0_72097710b3-9bfb4ab402-268310441

[135] WHO. FFPs Under Assessment. [Online]. [Cited 2018 Jul 5]. Available from: https://extranet.who.int/prequal/content/dossier-status

[136] Jabs DA, Holbrook JT, Van Natta ML, et al; Studies of Ocular Complications of AIDS Research Group. Risk factors for mortality in patients with AIDS in the era of highly active antiretroviral therapy. Ophthalmology [Online]. 2005 May [Cited 2018 Jul 5];112(5). Available from: https://doi.org/10.1016/j.ophtha.2004.10.049

[137] Tun N, Smithuis FM, London N, Drew WL, Heiden D. Mortality in patients with AIDS-related cytomegalovirus retinitis in Myanmar. Clin Infect Dis [Online]. 2014 Dec 1 [Cited 2018 Jul 5];59(11). Available from: https://doi.org/10.1093/cid/ciu648

[138] Holbrook JT, Jabs DA, Weinberg DV et al; Studies of Ocular Complications of AIDS (SOCA) Research Group. Visual loss in patients with cytomegalovirus retinitis and acquired immunodeficiency syndrome before widespread availability of highly active antiretroviral therapy. Arch Ophthalmol [Online]. 2003 Jan [Cited 2018 Jul 5];121(1). Available from: https://doi.org/10.1001/archopht.121.1.99

[139] Ford N, Shubber Z, Saranchuk P, et al. Burden of HIV-related cytomegalovirus retinitis in resource-limited settings: a systematic review. Clin Infect Dis [Online]. 2013 Nov [Cited 3018 Jul 5];57(9). Available from: https://doi.org/10.1093/cid/cit494

[140] Pathai S, Gilbert C, Weiss HA, McNally M, Lawn SD. Differing spectrum of HIV-associated ophthalmic disease among patients starting antiretroviral therapy in India and South Africa. Trop Med Int Health [Online]. 2011 Mar [Cited 2018 Jul 5];16(3). Available from: https://doi.org/10.1111/j.1365-3156.2010.02712.x

[141] Heiden D, Ford N, Wilson D, et al. Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. PLoS Med [Online]. 2007 [Cited 2018 Jul 5]4(12):e334. Available from: https://doi.org/10.1371/journal.pmed.0040334

[142] Shi Y, Lu H, He T, et al. Prevalence and clinical management of cytomegalovirus retinitis in AIDS patients in Shanghai, China. BMC Infect Dis [Online]. 2011 Nov 24 [Cited 2018 Jul 5];11(1). Available from: http://doi.org/10.1186/1471-2334-11-326

[143] Leenasirimakul P, Liu Y Jirawison C, et al. Risk factors for CMV retinitis among individuals with HIV and low CD4 count in northern Thailand: importance of access to healthcare. Br J Opthtalmol [Online]. 2016 Aug [Cited 2018 Jul 5];100(8). Available from: http://doi.org/10.1136/bjophthalmol-2016-308556

[144] Maningding E, Tun N, Chan KN, et al. CMV retinitis diagnosis by non-ophthalmologists: learning curve over a 4-Day training workshop. J Acquir Immune Defic Syndr [Online]. 2015 Jul 1 [Cited 2018 Jul 5]69(3):e115-7. Available from: http://doi.org/10.1097/QAI.0000000000000629

[145] Tun N, London N, Kyaw MK, et al. CMV retinitis screening and treatment in a resource-poor setting: three-year experience from a primary care HIV/AIDS programme in Myanmar. J Int AIDS Soc [Online]. 2011 Aug 15 [Cited 2018 Jul 5];14(1). Available from: http://doi.org/10.1186/1758-2652-14-41

[146] Medicines Patent Pool. Medicines Patent Pool and Roche sign HIV medicines agreement: focus on preventing blindness in people living with HIV. Press release. [Online]. 2013 Aug 5 [Cited 2018 Jul 5]. Available from: https://medicinespatentpool.org/mpp-media-post/medicines-patent-pool-and-roche-sign-hiv-medicines-agreement-focus-on-preventing-blindness-in-people-living-with-hiv/

[147] WHO. World Health Organization model list of essential in vitro diagnostics. 1st ed. [Online]. 2018 May 16 [Cited 2018 Jul 5]. Available from: http://www.who.int/medical_devices/diagnostics/WHO_EDL_2018.pdf