INTEREST 11
International Workshop on HIV Treatment, Pathogenesis, and Prevention Research in Resource-Limited Settings

Lilongwe, Malawi 16-19 May 2017
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Introduction

Lilongwe, Malawi was the host city for the 11th International Workshop on HIV Treatment, Pathogenesis, and Prevention Research in Resource-Limited Settings (INTEREST), held 16-19 May 2017. Malawi is a centre of excellence in HIV research and data were presented from several exciting projects that are taking place in the Heart of Africa, as Malawi is often called. As in the previous three years, the Workshop was dedicated to the memory of Professor Joep Lange and Jacqueline van Tongeren, who were pivotal in establishing the INTEREST meetings, and who tragically died when their plane (flight MH17) was shot down over the Ukraine on 17 July 2014.

A total of 506 delegates attended the Workshop: 264 Malawian healthcare professionals, researchers, students, and community members took the opportunity to participate actively in discussions, present their own research, and interact with HIV investigators from several other African countries (n=178), Europe (n=48), India (n=3), South America (n=2), and North America (n=11). Lively conversations took place during the formal sessions and the cultural and social events. Many delegates attended early morning events that were comprised of the Joep Lange career guidance sessions, poster discussions, and grantspersonship advice sessions led by EDCTP, NIH-Fogarty, and ANRS.

Jacqueline van Tongeren’s interests in the arts was reflected in the art installation by a local artist, Elson Kambalu, which was displayed during the Workshop, and in several demonstrations of Malawian dancing. The art installation, entitled ‘Between humans and a goal post’, called on all participants to ‘play the ball’ and to reflect on a single message about HIV that they could pass on to their communities. During an outreach event, the installation was displayed in a community in Lilongwe, where it generated much enthusiasm.

The Minister of Health for Malawi, the Honourable Dr Peter Kumpalume, opened INTEREST 11, welcoming all of the delegates and calling for everyone working in the HIV field to focus on the most efficient use of human and financial resources in order to end the HIV epidemic. He said that his ambition was that people living with HIV (PLHIV) should die with HIV and not from HIV.

HIV in Malawi

Epidemiology and management of HIV in Malawi

The population of Malawi grew from 12.4 million in 2004 to 17 million in 2017 (1). Analysis of the population demonstrates that the majority of Malawians are young (<34 years) and sexually active. The overall HIV prevalence in 2015-2016 was 10.6%, but this conceals both gender and geographical differences. HIV prevalence in women was 12.8% compared to 8.2%

1 Presentations are available http://www.infectiousdiseasesonline.com/11-interest/
2 EDCTP (European and Developing Countries Clinical Trials Partnership), NIH-Fogarty (US National Institutes of Health – Fogarty International Center), ANRS (France Recherche Nord & sud, sida-HIV, Hépatites)
3 Please note that the figures for HIV prevalence rates in various populations in Malawi published by the Ministry of Health, Malawi, and UNAIDS differ from those published in the Malawi population-based HIV impact assessment (PHIA). This is because the PHIA survey covered a different period from the government survey and the PHIA data were preliminary at the time of the INTEREST workshop.
in men. Infection rates were far higher in the south of the country compared to the north: ~16% vs. 7%. HIV prevalence was 18% in Blantyre City and 12% in Lilongwe. Malawi has set itself the goal of meeting, by 2020, the 90-90-90 targets and reducing the incidence of HIV infection to 0.2 (1, 2). It aims to end the HIV epidemic in the country by 2030. By the end of 2016, 82% of PLHIV knew their HIV status; 85% of HIV-positive PLHIV were on antiretroviral therapy (ART); and 88% of PLHIV on treatment had achieved viral suppression (1).

HIV testing
As HIV incidence falls, more targeted and increased efforts are required to find new cases of HIV in Malawi (1). The introduction of HIV Diagnostic Assistants in mid-2015 resulted in a greater number of HIV tests being conducted, but this did not translate into a greater number of HIV diagnoses.

HIV self-testing has been introduced in Malawi because it is unlikely that the 90% diagnosis goal will be met by conventional testing methods (3, 4). Self-testing avoids the potential for stigmatising encounters with healthcare professionals and can be carried out at a time and place of the person’s choosing. In Malawi, testing rates have increased in all age groups in men and women since self-testing was made available but the highest rate of uptake has been among adolescents (3). Nearly one half of people (44%) were first-time testers. Quality assurance carried out on 1,649 tests demonstrated a test sensitivity of 93.6% and specificity of 99.9%. No adverse effects of self-testing have been reported. Approximately half of self-testers who tested HIV-positive have linked to care and a three-fold increase in linkage has been documented if the person is assessed and ART is initiated at home.

Effects of Option B+ and Test and Treat in Malawi
Option B+ for prevention of mother to child transmission (PMTCT) was implemented in Malawi in mid-2011 (5). It resulted in an approximate two-fold increase in the number of women utilising PMTCT interventions between 2010 and 2012. Numbers continued to rise over the subsequent five years.

Test and treat was introduced in Malawi in 2016 (1, 5). There was an immediate and impressive increase in the number of men and non-pregnant women initiating ART but no change among pregnant women (Figure 1) (1, 5). The majority of the estimated 690,000 PLHIV in Malawi are on ART (69%)(6). The proportion of Malawians with viral suppression rose substantially in 2016, but there is still room for improvement in men aged over 30 years and women aged 20-34 years (1, 5). Most HIV-related mortality now occurs in PLHIV who are not on ART.
Overcrowding at HIV clinics has stimulated the introduction of differentiated care models in Malawi (6). The goals of this initiative are to: increase access to HIV care, especially by adolescent girls and boys, young women, and men of all ages; retain PLHIV in care; and improve the quality of HIV services in a more cost-effective way (1, 6). Services are adjusted to meet the needs of patients and providers, e.g. rapid ART initiation, less frequent clinic visits, more accessible services, task shifting of prescription refill services to health surveillance assistants, etc. Holding drop-in clinics at convenient locations and times is facilitating access for key populations and working people. Teen Clubs provide support and education, as well as health services, for adolescents. Monitoring and evaluation of differentiated care model services is ongoing to ensure that the goals are met without sacrificing patient care.

Progress towards the 90-90-90 goals

Introduction

Impressive progress is being made towards the 90-90-90 goals in sub-Saharan Africa, especially the second 90⁴, the treatment goal (2, 7). Prevention efforts have been scaled up and a 60% reduction in new HIV infections in children was observed between 2009 and 2015 (7). However, the number of new adult HIV infections has not fallen at the same rate.

Testing

In 2015, 62% of PLHIV in southern and eastern Africa knew their HIV status, compared to 36% in Western and Central Africa (7). Innovative and non-stigmatising methods of testing are therefore needed to reach the 90% ‘know status’ testing target (3, 4). Decentralised, home-based testing by lay counsellors has resulted in a rapid scale-up of testing services in southern and eastern Africa. However, confidentiality concerns have restricted further expansion of this service: people want privacy when learning their status and this is impossible if the lay counsellor is a member of their own community (3, 4). HIV self-testing offers the opportunity

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4 By 2020, 90% of all people living with HIV will know their HIV status. By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy. By 2020, 90% of all people receiving antiretroviral therapy will have achieved viral suppression.
for people who are not reached by other methods to ascertain their status. It has been well accepted by first-time testers, especially young people and men; women; repeat testers; key populations; and couples (3, 4). Additional interventions are needed after self-testing to link PLHIV to HIV care, HIV prevention (including voluntary medical male circumcision), and tuberculosis (TB) screening. Minimising the cost of the tests and improving distribution routes and linkage to care and prevention are needed to enhance the cost-effectiveness of self-testing (4).

Treatment

In sub-Saharan Africa, 47% of PLHIV were on ART in 2015, but this figure conceals considerable differences in ART coverage between regions (7). In southern and eastern Africa, 54% of eligible patients were on ART, while only 28% of PLHIV in western and central Africa were being treated (7).

Test and Treat, where ART is offered as soon as HIV has been diagnosed regardless of CD4 count, is now being implemented in many sub-Saharan African countries. Simplification of pre-ART care, treatment initiation, and counselling has facilitated scale-up of ART without imposing further burdens on over-stretched healthcare professionals (8). Rapid initiation is critical for the significant proportion of adults and children with advanced HIV disease who need to start ART urgently.

New treatment strategies, including novel drugs and/or formulations, are being evaluated (8). Effective, simple, once daily, and well-tolerated regimens that are taken as one tablet per day have facilitated the global roll out of ART. However, concerns are starting to emerge about the adverse effects of some widely used ARVs, such as tenofovir and efavirenz. Better tolerated first-line options that include dolutegravir, for example, are being considered. New strategies, such as long-acting formulations of antiretrovirals (ARVs), are also needed for some patients, e.g. to improve adherence. It is anticipated that the need for second-line ART will diminish as integrase inhibitors are more widely used in first-line regimens because it is believed that virological failure will be less common with these ARVs (9). Combinations of protease inhibitors and integrase inhibitors may provide nucleoside reverse transcriptase inhibitor (NRTI)-sparing options and be effective in the presence of resistance to NRTIs.

The potential of mobile health (mHealth) is being harnessed to enhance treatment success by providing HIV education and real time monitoring, supporting adherence, and reducing the need for clinic visits (10).

Viral Suppression

In 2015, 45% of PLHIV in sub-Saharan Africa on ART had achieved viral suppression, but this figure was only 12% in western and central Africa. Progress towards the goal of 90% of patients on ART achieving viral suppression is critically dependent on universal access to viral load (VL) testing so that patients can be tested on a regular basis (11).

Two presentations described VL testing scale-up in Kenya and Lesotho, respectively (12, 13). Viral load testing started in Kenya in 2008: one laboratory served four sites and 102 tests were performed that year (12). In 2016, there were 1.5 million Kenyans living with HIV, of whom approximately a million were on ART. Seven laboratories carried out 442,227 VL tests in the country in 2016. It was reported that 1.479 million tests could be undertaken each year with the 2016 capacity. Despite the rapid expansion of testing facilities, it is predicted that more VL capacity will be required by 2019 when 1.9 million tests per year will be needed. Dried blood spot (DBS) samples have been evaluated for VL testing in Kenya: the results were
acceptable in terms of stability and accuracy. Adopting this option will enable peripheral facilities to send samples to central laboratories and increase access to VL testing.

Lesotho adopted Test and Treat in 2016 and intends to achieve the 90-90-90 targets in five districts by the end of 2017 (13). Targeted VL monitoring was introduced in 2014 for patients who were failing ART; on second- or third-line ART; children <5 years; and pregnant and breastfeeding women. Since June 2016, all patients on ART in Lesotho have been able to access VL testing. By the end of 2017, the scale-up of laboratory facilities should enable >90% of patients on ART to access VL testing. The referral network has been strengthened and the frequency of sample collection from health centres increased. The VL Roche platforms at the National Reference Laboratory are used now for 16 hours per day. Decentralised VL testing is being implemented at district laboratories. DBS based VL testing is being introduced in hard to reach areas of Lesotho and steps are being taken to ensure uninterrupted VL testing services. One of the key issues is to ensure that VL results are sent to the clinics in a timely manner so that patients can be managed appropriately.

Population health assessments and country responses
Population-based HIV impact assessments (PHIA) have been carried out in Malawi, Zimbabwe, and Zambia using common methodologies so that the results can be compared and combined to increase the power of the analyses (14). The three countries are geographically contiguous, have similar population size, and are experiencing generalized clade C HIV epidemics. The primary objectives of the PHIA were to estimate national HIV incidence rates and sub-national prevalence of VL suppression in adults.

In all countries, the survey response rate was lower among men than women, but men who had agreed to be interviewed were just as willing to undergo HIV testing as women. HIV prevalence in women was higher than in men in the three countries (Figure 2)\(^5\). HIV prevalence in children of both genders was similar in Malawi, but slightly higher for males than for females in Zambia and Zimbabwe.

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\(^5\) Please note that the PHIA figures for HIV prevalence in various populations in Malawi differ from those published by the Ministry of Health, Malawi, and UNAIDS. This is because the PHIA survey covered a different period from the government survey and the data were preliminary at the time of the INTEREST workshop.
Viral suppression was detected in the majority of PLHIV in all three countries (59-67.7%), with women achieving slightly higher levels of viral suppression than men. Progress towards reaching the 90-90-90 goals by 2030 is very encouraging (Figure 3).

Figure 2: Adult HIV Prevalence in Malawi (MPHIA), Zambia (ZAMPHIA) and Zimbabwe (ZIMPHIA)

![Figure 2: Adult HIV Prevalence in Malawi (MPHIA), Zambia (ZAMPHIA) and Zimbabwe (ZIMPHIA)](image)

Figure 3: Progress towards 90-90-90 goals in Malawi (MPHIA), Zambia (ZAMPHIA) and Zimbabwe (ZIMPHIA)

![Figure 3: Progress towards 90-90-90 goals in Malawi (MPHIA), Zambia (ZAMPHIA) and Zimbabwe (ZIMPHIA)](image)

The PHIA data have been utilised in National AIDS Strategies and to develop HIV policies and programmes (15). Continued investment in health systems is necessary to consolidate and maintain the health gains already achieved. Given the stabilization and even reduction of donor funding for HIV in recent years, it is essential that domestic funding for HIV programmes in sub-Saharan Africa increases (16). Innovative methods of raising funds and ring fencing tax receipts for HIV, including AIDS Trust Funds and levies on infrastructure
spending, are under consideration or being established. Given the limited size of the formal economy in many sub-Saharan countries, levies that raise money from the informal sector are also needed.

During the INTEREST meeting, several speakers warned that the current gains in HIV control must be protected and sustainable interventions must be implemented to ensure that the 90-90-90 goals are met and the AIDS epidemic is ended. There is a window of opportunity between 2017 and 2020 to dramatically reduce new HIV infections, but this will only be achieved if Fast-Track tactics, as recommended by UNAIDS, are adopted (17).

Meeting the needs of key populations

Key populations are at particular risk of HIV infection

In 2015, key populations in sub-Saharan Africa accounted for 20% of new adult HIV infections, demonstrating that there are concentrated key population epidemics within the context of generalised epidemics driven by heterosexual transmission (18). Key populations are at a much greater (10-49 times) risk of becoming infected with HIV than the general population (19). Key populations at highest risk of HIV exposure include: men who have sex with men (MSM), people who inject drugs (PWID), sex workers (SW), transgender people, migrants, prisoners, and their sexual partners. Young women in southern Africa, who are also at extremely high risk of HIV exposure, are addressed later in this report. HIV prevalence among MSM is rising, both globally and in sub-Saharan Africa. HIV prevalence in SW in southern Africa is 10-20 times higher than in the general population (18).

In Malawi, HIV prevalence rates in female SWs and MSM were 69% and 18.2%, respectively, compared to 9.1% in the general adult population (2016 data). Levels of knowledge of HIV status and linkage to care are very low in MSM. HIV-related deaths have tripled since 2000 in adolescents, with AIDS now the second cause of death in this age group globally (18). HIV prevalence in prisoners in sub-Saharan Africa ranges from 2.3% to 34.9%, levels that are almost always higher than in the general population.

Data on HIV prevalence in transgender populations in Africa are limited, but high HIV prevalence has been reported in Asia, e.g. 19.3% in Kuala Lumpur, Malaysia and 30.8% in Jakarta, Indonesia (19). Transgender women are at particular risk of HIV infection if they have multiple sexual partners, unprotected anal intercourse, experience depression, undergo unsafe hormone and silicone injections, sell sex, or take drugs before sex (20). Stigma, discrimination, and lack of legal recognition of transgender people are major barriers to accessing healthcare and prevention services. This marginalisation also increases the likelihood of risky behaviour.

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6 Key populations are those that are key to the epidemic’s dynamics and key to the response. UNAIDS considers gay men and other men who have sex with men, sex workers and their clients, transgender people, people who inject drugs, and prisoners and other incarcerated people as the main key population groups. Their engagement is critical to a successful HIV response everywhere. The term key populations at higher risk also may be used more broadly, referring to additional populations at higher risk of acquiring or transmitting HIV based on the epidemiological and social context.

Despite the considerable needs of key populations, their access to HIV services tends to be inadequate or non-existent, which makes it very challenging to halt epidemics in these populations (18). Criminalisation, stigmatisation, discrimination, and the lack of appropriate services are all drivers of HIV transmission in key populations.

**How can key populations be protected from HIV infection?**

Improving HIV literacy in all key populations is an important factor in protecting them from HIV infection (18). Young members of key populations are at particularly high risk of infection and need tailored information that addresses their questions.

Many barriers to HIV prevention services exist. In prisons, for example, there is a lack of continuity of care between different prisons and between prisons and the community. Overcrowding in African prisons, high HIV prevalence, and criminalisation of sex between men preventing condom provision to prisoners, all facilitate HIV transmission in this setting.

Harm reduction programmes for PWIDs are non-existent, or very limited, in most sub-Saharan countries. Provision of opioid substitution therapy (OST) and needle-syringe programmes is minimal in this region and this increases the risk of HIV transmission between PWIDs and their sexual partners. In Canada, where harm reduction and treatment-as-prevention programmes have been implemented for PWID living with HIV, PWIDs have experienced substantial declines in HIV incidence. Political will and access to resources are essential to implement these prevention initiatives. Criminalisation and stigmatisation of both sex work and sex between men are common in sub-Saharan Africa, which severely restricts access to sexually transmitted infection (STI) treatment, condoms, and medical care.

Innovative treatment and prevention programmes, as well as outreach testing, are all essential to reach key populations and to prevent the epidemic being driven underground (18). Overcoming multiple types of stigma (external, internalised, and anticipated stigma) is challenging, but it is essential if key populations are to access HIV services. In general, attitudes towards PLHIV and MSM appear to be changing in many societies, but progress is slow in some communities.

The use of information technology and smartphones to reach key populations and provide mHealth is in its infancy, but can provide confidential, interactive, and tailored information that may help individuals at risk to access services and/or be retained in care with a low risk of stigma (10). HIV self-testing can be used to individuals at high risk of HIV exposure who are reluctant to attend clinics due to concerns about confidentiality (3). In South, the Iyeza Express bicycle delivery service that delivers chronic medication to patients who are unable or unwilling to go to health facilities is expanding its services to deliver HIV self-tests (18).

Encouraging data have emerged from key population initiatives. Widespread provision of pre-exposure prophylaxis (PrEP) in San Francisco has resulted in 10-15% of people at high risk of HIV exposure, particularly MSM, using this protective measure. In India, 83% of SWs have accessed HIV prevention programmes despite sex work being illegal and the existence of widespread stigma and discrimination against sex work (18). As a result, HIV prevalence in Indian SWs has fallen.
**Access to HIV care for key populations**

Best practices in HIV care for key populations have the following characteristics in common (18):

- Adoption of a public health approach.
- Population-specific services and harm reduction strategies.
- PrEP for key populations to protect individuals and their sexual partners.
- Innovative approaches such as self-testing and mHealth.
- Personal contact between healthcare professionals and PLHIV as this reduces stigma and discrimination.
- Tailored, client-centred services.
- Protection of human rights.
- Provision of social justice and an appropriate legal framework.

Comprehensive packages of HIV services that are appropriate for transgender people can be developed and have been shown to be effective (20). Addressing stigma and ensuring that supportive legislation, policies, and financial arrangements are in place are essential for successful service delivery. Community empowerment and addressing violence against people from key populations are also key factors. Many transgender people prioritise use of hormone therapy over HIV treatment. It is therefore considered essential for healthcare professionals to be aware of potential drug-drug interactions and manage patients appropriately.

Harm reduction programmes are starting in some sub-Saharan African countries, such as South Africa and Kenya. However, there is limited political and financial support for these programmes, despite evidence of their effectiveness in reducing the risk of HIV infection in PWID (18). OST and needle-syringe programmes were introduced in Mauritius in 2006, when PWID accounted for 92% of new HIV infections. In 2011, OST was extended to prisons. When a new government was elected in 2014, the harm reduction programmes were discontinued and, for the first time in a decade, HIV incidence increased in PWID from 31% in 2014 to 35% in 2015. This demonstrates that HIV epidemics can only be controlled by ongoing and sustained HIV programmes for key populations.

Decriminalising sex work, eliminating sexual violence, and increasing ART coverage among SWs in Kenya would substantially reduce HIV incidence among both female SWs and their clients (18). South Africa has promised to supply PrEP for 3,000 SWs, using mobile units to supply it and other HIV, TB, and STI services in communities, in an attempt to protect them and their clients. Healthcare professionals are being trained to not discriminate against SWs and to be sensitive to their needs. Linkage to care reached 57% in 2015.

HIV services (diagnosis, treatment, and monitoring) for people at risk of imprisonment and those already in prisons are starting to develop in a number of sub-Saharan African countries (18). The aim is to provide care both inside and outside of the prison environment. Peer education and provision of condoms have been introduced in some prisons. Despite the potential of PrEP and post exposure prophylaxis (PEP) to protect prisoners from infection, access to these interventions is almost non-existent.
There is a high level of interest in PrEP among MSM in South Africa and demonstration projects have yielded encouraging data about acceptability and adherence (18). Linkage to care, however, has been low, even in cities with high quality and accessible HIV services.

Reaching the ‘last 10%’ will require innovative, creative, and dispersed HIV services that engage with key populations and go beyond healthcare. Services have to be confidential, appropriate, efficient, relevant, and client centred.

Testing and treatment of men

Introduction

HIV testing and treatment of men has historically lagged behind that of women. Numerous barriers that prevent men from accessing HIV services have been identified, with stigma being a major factor. There is a clear need for men-friendly, easily-accessible clinics with flexible opening times so that men can access them without losing paid work and/or incurring high transportation costs.

Innovative testing options are needed for men – potential of self-testing

Self-testing is attractive to men because of its confidentiality and flexibility (4). They find it more acceptable to self-test in the privacy of their own homes than risking stigmatising encounters at clinics or workplace testing sites. Self-testing can also be used to promote couples testing (3, 4). So far, these has been no evidence of an increased risk of potential adverse effects of self-testing, such as intimate partner violence, homicide, or suicide (3). Linkage to care, once diagnosed, is 42-56%. A small proportion of respondents (3%, 287/10,007) in a study conducted in Malawi reported that they had been ‘forced to test’ by their partner, but 94% of these individuals also said that they would recommend self-testing to their friends and relatives.

Treatment of men living with HIV

Involving men in HIV prevention and treatment programmes is critical to the success of halting HIV transmission (5, 21). Factors that increase the likelihood of men participating in HIV care include decentralized health facilities so that most people can walk to them, routine 3-6 month appointments rather than monthly clinic visits, and elimination of diagnostic hurdles (CD4 cell count, VL) prior to starting therapy (Test and Treat) (5). Incentives to encourage men to attend antenatal clinics, e.g. fast track appointments for women who attend with their partners, have been partially effective but have also had unwanted effects, such as the phenomenon seen in Malawi of ‘husbands for hire’. However, implementing Option B+ in Malawi, for prevention of mother-to-child transmission and keeping mothers alive, resulted in a 25% increase in the number of men starting ART (5). Implementing Test and Treat resulted in a ‘wave’ of men who were already in pre-ART care initiating ART. It is not yet clear if this increase will be maintained in the long term. In 2016, ~55% of men in need of ART were being treated in Malawi. It is particularly important that men living with HIV aged 30-44 years are successfully treated since they are more likely than younger men to transmit HIV to young women. Partner testing and counselling leads to better uptake of, and adherence to, ART. Treating HIV-positive men prevents father-to-(HIV-negative)-mother-to-child HIV transmission. It is anticipated that universal Test and Treat will reduce the overall population VL, which will help protect everyone from infection.
HIV-related issues affecting adolescents and young adults

Overview
INTEREST 11 addressed a number of issues affecting adolescents and young adults living with HIV, especially in resource-limited settings. This large and growing population group is heterogeneous, with diverse needs and experiences. Some young people are in school, some are working formally or informally, and yet others are unemployed. Some are in stable sexual partnerships, some have sequential relationships, and some have non-exclusive relationships, while others are not sexually active. Some are already parents and some are caring for siblings, while others have no childcare responsibilities (21). This diversity underpins the importance of involving young people in the design of HIV prevention, treatment, and care and support HIV services that are tailored for their individual needs. It highlights the importance of differentiated care and service delivery (www.differentiatedcare.org) rather than ‘one size fits all’ (22). Addressing the determinants of stigma and discrimination, including internalised stigma, is critical to enhancing the health and well-being of adolescents and young adults everywhere, regardless of HIV status.

HIV prevention
Young women (15-24 years) bear a disproportionate burden of HIV infection in southern and eastern Africa. They are up to eight times more likely to acquire HIV than are young men; almost three-quarters (74%) of young people in this age group living with HIV in sub-Saharan Africa are girls or young women (21, 23). The UN Political Declaration on Ending AIDS set the goal of reducing new infections in adolescent girls and young women to ≈100,000 by 2020 (21). Among the many barriers standing in the way of achieving this objective is suboptimal comprehensive HIV knowledge and condom use among young sub-Saharan African women. In rural KwaZulu-Natal, South Africa, more than 30% of pregnant women are under 20 years of age and one in five of these women already has HIV (23). By the age of 23 years, half (50%) of pregnant women in this region have HIV. If a woman’s partner is 4 or more years older than she is, she has a risk of acquiring HIV infection that is from 4 to 8 times higher than if her partner is of a similar age. HIV infection studies among high school students in rural KwaZulu-Natal demonstrate that girls, especially those with older sexual partners, are more likely to be HIV-positive than boys of their age. Despite reporting a low frequency of sexual activity, girls and young women are more likely to engage in unprotected sex when they are sexually active. The dynamics of HIV transmission in this population have been studied using phylogenetic analyses (23). They show that young women under age 25 years are acquiring HIV from older men (25-40 years), who themselves are often also in a relationship with a woman of their own age. Younger women mature into the older cohort of women aged 25-40 years, when they then transmit HIV to similarly-aged male partners.

A community study in an urban and rural area of the Eastern Cape investigated secondary HIV transmission among South African adolescents (24). Data were obtained from a longitudinal panel study of 1060 HIV-positive and 467 HIV-negative adolescents, as well through qualitative research conducted with 80 youth. The majority of the participants in the longitudinal panel lacked basic necessities (68%) and 90% were orphans (44% maternal orphans, 30% paternal orphans; 16% double orphans). A third (33%) did not know their HIV status. One quarter of the sample reported at least one high-risk sexual practice in the previous year. Non-adherence to antiretroviral treatment (ART) was self-reported by 36% of the young people living with HIV. Twelve percent of those living with HIV reported both
unprotected sex and non-adherence to ART, placing them at high risk of ongoing secondary HIV transmission.

The CAPRISA 004 study demonstrated that presence of genital inflammation prior to HIV exposure rendered women more vulnerable to HIV acquisition (Odds Ratio: 3.2, 95% CI 1.3-7.9) (23). If *Prevotella bivia* bacteria were present in the vagina, the risk of genital inflammation was 19 times higher and the risk of acquiring HIV was 13 times higher than if they were absent. The composition of the vaginal microbiome appears to affect the efficacy of pre-exposure prophylaxis (PrEP) using tenofovir: if *Lactobacillus* was the dominant vaginal microbe, tenofovir vaginal gel PrEP was 78% protective compared to 26% when non-*Lactobacillus* strains dominated. *In vitro* experiments have demonstrated that tenofovir is rapidly depleted by *Gardnerella* strains but not by *Lactobacillus* (3).

Young women need choices to interrupt the cycle of HIV transmission, including PrEP, voluntary medical male circumcision (VMMC), antiretroviral therapy for all PLHIV, and improved methods of HIV counselling and testing, such as self-testing which is well accepted by adolescent girls (3, 4, 21, 23). If confirmed in further studies, vaginal probiotics to enhance *Lactobacillus* dominance may reduce HIV risk and enhance PrEP efficacy. Two trials of vaginal dapivirine rings (replaced monthly) reported moderate effectiveness in older women but not in those under 25 (21, 25, 26). This may have been due to lower adherence associated with low risk perception, differences in vaginal microbiome, or other factors. Multipurpose technologies, such as combination contraceptive and HIV prevention devices, may be more attractive to young women and thus improve adherence (21). Trials of such devices are only just beginning in small numbers of women.

The DREAMS programme aims to reduce HIV incidence in adolescent girls and young women in prioritised areas by 40% in three years (21). Tailored programmes include male and female condom provision and promotion, HIV testing (including self-testing), post-violence care, contraceptive methods, social asset building, PrEP, school-based HIV and violence prevention programmes, family strengthening initiatives, and male sexual partner-focused strategies to reduce HIV transmission, including VMMC. The best outcomes are being observed when a young woman utilises at least six of these support mechanisms.

**Second- and third-line options for children and adolescents**

The WHO recommendations for second-line ART regimens for children and adolescents depend on the initial regimen taken (11). In all second-line regimens, a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone is utilised, with the third drug from a class different to that in the first-line regimen. Comparing responses to second-line ART can be challenging because of variations in the definitions of virological failure and duration of follow-up used in clinical studies (27). A Ugandan study of second-line ART (2 NRTIs plus lopinavir/ritonavir) in 60 children <12 years old demonstrated virological success (pVL <1000 copies/mL) in ~80% of patients at 24 months (28). No mutations associated with resistance to protease inhibitors were detected in the small number of virological failures that occurred, and all patients were able to regain virological control after adherence counselling.

The major factors associated with second-line treatment failure in children and adolescents are poor adherence, presence of physical wasting at the start of second-line ART, having AIDS prior to first-line ART, baseline CD4 cell count less than 100 cells/mm$^3$, having virological failure prior to adolescence, initiating ART as an adolescent, and non-disclosure of HIV status
Having a grandparent as a caregiver or not having a caregiver at all were also associated with virological failure. Medication factors included adverse events, poor palatability, initial non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen, and drug-drug interactions. Health system factors associated with second-line failure included stock outs, limited VL monitoring, long waiting times at clinics, and poor healthcare worker knowledge and attitudes. Social factors, such as stigma, long distances to clinics, cost of transport to clinics, and lack of food, also increase the risk of second-line failure. All of these factors interact: risk of virological failure increases as the number of adverse factors experienced by a young person living with HIV rises.

The WHO recommends darunavir/r and/or raltegravir (or dolutegravir) with (or, in specific cases, without) 1-2 NRTIs as third-line therapy for children and adolescents (11). In settings where it is possible to perform resistance testing, the presence of drug resistance mutations (DRMs) can be used to predict susceptibility to third-line ARVs (27). Initiatives such the New Horizons programme are increasing access to second- and third-line antiretroviral drugs (ARVs) and provide educational and capacity building support. Of five children who had benefited from this programme, all had achieved virological suppression on their third-line ART regimen (follow up: 6-54 months) (27).

Supporting adherence to treatment regimens
Adolescent girls in sub-Saharan Africa tend to have low rates of adherence to ART and, consequently, sub-optimal levels of viral suppression (21). Among the adherence support measures for caregivers of children living with HIV and for adolescents themselves are medication reminders, pill boxes, cell phone messages (appointment and medication reminders), peer support groups, timely disclosure of HIV status, and socioeconomic support (27).

Risk factors for secondary HIV transmission from young people are alcohol use, stigma, food insecurity, having been horizontally infected with HIV, and being in a relationship. Adolescents with three or more of these risk factors were highly likely to transmit HIV (24). Providing social support, food, and closer monitoring reduced the risk of non-adherence by at least 50%. Programmes that address these issues can help improve adherence and reduce secondary HIV transmission.

Use of digital technologies to reach adolescents
Rural adolescents face particular challenges in accessing healthcare: the clinic may be a long way from the young person’s home and finding the money and time to travel there can be very difficult. mHealth services can help young people in such settings: weekly text message medication reminders and real-time monitoring strategies can improve outcomes (10). In sub-Saharan Africa, the majority of adolescents own a mobile phone or smartphone: in one study, 64% of 16-18 year olds owned a phone or smartphone (10). Smartphone sales are forecast to grow by 40% per year in this region (10). Although adolescents use phones predominantly for messaging, music, and games, they are also accessing information about health, HIV, and employment using their phones.

Development is underway of more mHealth applications (apps) that respond to adolescents’ needs (both HIV-related and other issues) and are relevant to local conditions is underway (10). Emojis, educational gaming, and avatars make apps more attractive. Involving adolescents in designing and updating apps is essential. Chat apps can provide support and information in an anonymous setting, which diminishes the risk of potential stigmatising
encounters with professionals or lay counsellors (10, 29). Electronic monitoring of symptoms reduces the need for frequent clinic visits, which is beneficial for both young people living with HIV and healthcare professionals (10). Loss to follow-up can be reduced through ongoing regular communication between adolescents and healthcare workers. The use of digital cash apps for health savings and healthcare in countries such as Kenya, and electronic medical records in places such as Cape Town, South Africa, are enhancing HIV health care for everyone, including adolescents and young people.

**Transition of adolescents living with HIV to adult care – differentiated care**

As adolescents transition from being dependent children to independent adults, their healthcare needs are changing from paediatric to adult care at a time that they are also facing many other challenges (Figure 4) (30, 31). This period is fraught with potential difficulties for adolescents living with HIV, including non-adherence, poor viral suppression, mental health problems, stigma, high loss to follow up, and an enhanced risk of AIDS mortality. It is also a time when secondary HIV transmission to sexual partners and to offspring is high; addressing these routes of transmission is essential to break the cycle of HIV infection (31). Interventions such as delaying child bearing until an adolescent living with HIV is in a stable relationship and is on successful ART can dramatically reduce the risk of onward HIV transmission.

*Figure 4: Issues faced by adolescents living with HIV as they transition to adult care*

![Diagram showing transition from children to adults, with adolescents dealing with adherence, disclosure, drugs, employment, finances, and gender identity, to housing, peers, mental health, support networks, school, and retention.]

The International AIDS Society, in association with the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER), has produced a special supplement on adolescent transition (32). The differentiated care and service delivery model provides a framework to design healthcare and psychosocial services that meet adolescents’ needs for HIV prevention and treatment (22, 31). Adolescent retention in care is improved through accessible weekend clinics that provide ART refills, healthcare, and psychosocial support (31). Teen Clubs have

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proved very popular and effective in Malawi. Adherence and viral suppression among adolescents who attend these clubs are equivalent to those seen in adult clinics, with adolescent therapeutic outcomes superior to those seen in adolescents who do not attend Teen Clubs. The success of Teen Clubs is anchored in their responsiveness to adolescents’ needs: preparing adolescents for life while being a forum for meeting friends. No waiting times and minimal or zero transport costs make clubs attractive to adolescents living with HIV.

In Malawi, the Transition Training (T²) programme for young adults (18-24 years) who have graduated from secondary school has been developed by adolescents living with HIV and volunteers (31). It includes the T² Tool Box. This set of tools provides education and support for self-healthcare, along with life skills for employment and education. Knowledge of a range of HIV, sexual health, personal skills, and employment topics increased substantially after attending ten sessions of the T² programme. Adherence and viral suppression were considerably higher in programme graduates than in adults attending the local clinic. The T² programme encouraged adolescents living with HIV to transition from Teen Clubs to become mentors to younger adolescents, which facilitates adolescent HIV programme sustainability. Innovative methods of HIV prevention, care, and treatment service delivery to adolescents and young adults will help to prevent HIV infection and ensure effective treatment for those living with HIV.

Co-morbidities update

TB – improvements in diagnostics
The diagnosis of tuberculosis (TB), especially in co-infected HIV/TB individuals, is an important opportunity to identify and treat a condition that is associated with a high burden of morbidity and mortality (33-35). The GeneXpert assay has been described as the most important advance in the diagnosis of TB in a century (33). However, its use has not improved morbidity and mortality outcomes in intervention trials (36). There is still an unmet need for simple diagnostic TB tests that can be used in community settings. The clinical potential of the lipoarabinomannan (LAM) TB diagnostic assay was discussed during INTEREST 11 (33). LAM is a lipopolysaccharide mycobacterial cell wall structural component that has immunogenic and immune modulatory activity (Figure 5) (33). The Alere Determine™ TB LAM Antigen (TB LAM LFA) Lateral Flow Test incubates 60 µL of urine for 25 minutes at room temperature. The test strip is then compared with the reference scale. In a 2015 World Health Organization (WHO) review, the overall agreement between TB-ELISA and TB LAM LFA was 507/516 (98.3%, 95% CI: 96.7-99.2), giving a Kappa value of 0.84 (95% CI 0.72-0.92). Inter- and intra-reader variability was considered to be high.
The LAM LFA has numerous advantages: low cost ($3.50/test), point of care (POC) use, ease and safety of obtaining a urine specimen compared to sputum expectoration or induction, availability of results in 25 minutes, simplicity of the read out with no hardware required, rapidity of diagnosis supporting rapid treatment decisions, and minimal biosafety concerns (33). However, a number of factors affect the sensitivity of the assay: the choice of reference standard, the cut-off thresholds, observer variability, urine concentration, variable storage conditions, urine contamination, and the population being studied. These limitations led WHO to advise in 2015 that LAM should not be used for TB diagnosis and screening, but that it could be used to assist in TB diagnosis in very immunocompromised or seriously ill HIV-positive patients with signs and symptoms of TB (www.who.int/tb/areas-of-work/laboratory/policy_statement_lam_web.pdf). Since 50% of co-infected patients who die from TB have not been diagnosed with TB prior to death, it is critical that better diagnostic methods are developed to identify TB in this population.

A Cochrane review of the accuracy of LAM LFA for the diagnosis and screening of active TB disease in HIV-positive adults has shown that the test has low sensitivity for diagnosis in HIV-positive adults or screening, but has utility in seriously ill patients (37). This has stimulated research into the source of LAM antigens in seriously ill, co-infected patients. It became clear that dying mycobacteria were not the major supply of the antigens and there was no evidence of significant protein leakage through the renal glomerulus. An analysis of renal histology in a cohort of HIV-positive adults in Uganda demonstrated that renal TB was present in 8/13 LAM+ patients, even though 7/13 LAM+ patients were not on anti-TB therapy at the time of death (38). Renal TB accounted for LAM positivity in the majority of patients. However, some patients with disseminated TB but without renal involvement were also LAM+, suggesting that other mechanisms could be responsible for urinary LAM positivity in a minority of patients.

A comparison of sputum- and urine-based diagnostic assays for HIV-associated TB demonstrated that urine LAM was 100% sensitive in very anaemic patients (haemoglobin <8) but was less sensitive in those with haemoglobin >8 (39). Renal TB occurs in very sick HIV/TB co-infected patients and is strongly associated with a very poor prognosis. There is, therefore, a rationale for routine urine LAM testing in sick, hospitalised HIV-positive patients to identify...
TB co-infection and facilitate rapid initiation of TB therapy. This concept is being evaluated in a three-year study - Screening for Tuberculosis to Reduce AIDS-Related Mortality in Hospitalized Patients in Africa (STAMP) that started in 2015. STAMP is a randomized controlled trial to assess the clinical outcomes of standard sputum-based testing with GeneXpert MTB/RIF plus additional urine-based LAM screening compared to standard screening alone.

Community-based HIV testing campaigns by lay health workers have been used to identify people with six self-reported signs and symptoms of TB in Botswana (34). The signs/symptoms of TB (SSTB) were: cough or fever for more than a two-week duration; lymphadenopathy; haemoptysis; night sweats; or unexplained weight loss. Everyone with SSTB was referred to a community clinic, regardless of their HIV status, and linked to care. Compared to PLHIV without SSTB, PLHIV with SSTB were more likely to be newly diagnosed with HIV, not on ART, and to have a family member with TB. This study demonstrated that community-based HIV and TB case identification by lay health workers was feasible and resulted in the identification of many people with TB, especially co-infected PLHIV, who were linked to care for both HIV and TB.

GeneXpert is being used in Malawi to diagnose TB among PLHIV with presumptive TB. The results of a cross-sectional analysis of routine healthcare data collected between April 2014 and June 2016 in 21 TB/HIV integrated clinics in Malawi were presented at INTEREST 11 (35). Over this period, the proportion of HIV-positive people who were also presumptive TB cases increased. However, coverage of GeneXpert was sub-optimal: <50% of PLHIV. The investigators recommended that all PLHIV who are suspected of being co-infected with TB should have access to GeneXpert and start TB treatment immediately if pulmonary TB is diagnosed.

**Hepatitis B**

More than 50% of liver-related mortality associated with hepatitis B (HBV) or C (HCV) globally occurs in sub-Saharan Africa (40). North Africa, particularly Egypt, has the highest prevalence of chronic HCV infection in the world9. In Uganda, where 52.3% of people have been exposed to HBV, the overall prevalence of HBV chronic infection is 10%. These figures conceal wide disparities between regions in terms of HBV prevalence: levels of 23.9% have been observed in the north west compared to 3.8% in the south east. HBV is transmitted primarily by horizontal routes (mainly sexual contact). People with high levels of HBV DNA are more likely to transmit than those with low HBV DNA levels. In areas where HBsAg (HBV surface antigen) prevalence is >2%, vertical transmission from mother to baby is common. Occult HBV infection has been identified in 30% of patients admitted to the emergency room in Mulago (94/314 samples), suggesting that HBV could be transmitted via blood transfusions in Uganda. Treatment options for HBV mono-infection are limited in sub-Saharan Africa and liver transplantation is not available. HBV has been shown to induce hepatocellular carcinoma (HCC) in young adults: data from patients managed at 14 centres across Africa have been analysed. The most frequent age range at HBV-related HCC diagnosis in non-Egyptian African centres was 32.5-37.5 years, which is ~20 years younger than in Egypt. The median survival

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was 2.5 months in non-Egyptian African centres, compared to 10.9 months in Egypt (p<0.01). The WHO has developed its first ever Global Strategy on Viral Hepatitis 2016-2021, which aims to eliminate viral hepatitis as a major public health threat by 2030. Increased access to HBV testing, vaccination, and treatment, as well as education of the public and healthcare professionals, are essential to reach this goal.

HIV/HBV co-infection is the cause of growing health problems in sub-Saharan Africa (41). Infection with both viruses leads to complex immunological interactions that result in increased fibrosis and sub-optimal immune responses to HBV, which mean that the virus is not cleared even with tenofovir treatment. In resource-limited settings, access to HBsAg testing is limited; as a result, many co-infected patients are not identified. There is little information about the natural history of co-infection in these settings. Inadequate access to HBV vaccination, liver disease fibrosis assessment methods, and virological monitoring of HBV DNA compromises the ability of healthcare professionals to prevent and treat HBV infection and prevent disease progression. Advocacy efforts are ongoing to improve awareness of HBV; increase government commitment to preventing and treating HBV; extend coverage of diagnostics, prevention and treatment options for HBV; and promote the WHO Global Strategy (42).

End-of-life and palliative care
End-of-life and palliative care have not traditionally received much attention in sub-Saharan Africa healthcare systems (43). In 2003, the African Palliative Care Association (APCA) was set up to address this issue: its vision is to achieve access to palliative care for all in Africa. APCA supports programmes in 29 African countries and works to ensure that palliative care is integrated into health systems at all levels. Increasing knowledge and awareness of palliative care among all stakeholders and building the evidence base for palliative care in Africa are key strategic objectives. APCA offers technical assistance to Ministries of Health and relevant stakeholders in relation to policy development; education; essential medicines and technologies; implementation of service delivery framework standards; organisational development; and research. National palliative care policies have been developed in 8/54 African countries, thanks to APCA’s support. The philosophy is: ‘In palliative care, it is good to hope for the best but prepare for the worst’. Comprehensive planning and good communication are the keys to good end-of-life care. In most African countries, comprehensive formal end-of-life care cannot be provided, and so it is necessary to use family and community resources in conjunction with professional support to achieve a holistic and optimal end-of-life experience for the patient and family.

Conclusion
During the closing session, the winner of the Joep Lange Award was announced. It was Augustine Choko of Malawi who had presented very positive and interesting data on One year outcomes following availability of HIV self-testing in Blantyre, Malawi (3). The chairs of the meeting praised the spirit and liveliness of the Workshop, as well as the high-quality data that had been presented by all of the speakers. They thanked the Workshop sponsors, the local organising committee, the international and scientific committees, and all of the people who had made the meeting a success. The location of INTEREST 12, to be held in 2018, will be announced shortly.
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