Key Data from AIDS 2022

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Abstract (38 words)

In this paper we aim to report on the highlights of the AIDS 2022 conference, addressing three main themes: HIV Targets and Cascades, HIV and sexually transmitted infection (STI) prophylaxis, and HIV Treatment including the use of antiretroviral therapy in pregnancy.

Introduction

AIDS 2022 was held in Montreal, Canada as a hybrid meeting from 29 July to 02 August. The conference, and its inherent noisy and colourful protests, offered a much-needed blast of real-life energy to those able to attend. Sadly, visa denials and delays left many unable to attend, resulting in empty chairs on panel discussions and raising questions about the appropriateness of this global meeting being held in high-income countries (1).

We cover some of the highlights of the programme:

- HIV Targets and Cascades
- HIV and sexually transmitted infection (STI) prophylaxis
- Antiretroviral Therapy

HIV Targets and Cascades

The most recent UNAIDS HIV targets, to be achieved by 2025, aim to ensure that 95% of all people living with HIV, in all populations and sub-groups, should be aware of their HIV status, 95% of those should be on antiretroviral therapy (ART) and 95% on those on ART should be virally suppressed (2). However, data from 9 countries in Africa presented at the meeting showed that the proportion of people diagnosed late remains stubbornly high: 43% overall, ranging from 30% in Uganda to 53% in Zimbabwe (3). Risk factors for late HIV diagnosis included older age, male gender and having never tested for HIV previously. The authors called for a number of interventions to reduce late diagnosis including supporting men to better access healthcare (including HIV testing) and improving HIV testing with expanded community HIV testing.

However, there was also good epidemiological news! Botswana, the first country in Africa to offer free ART to people living with HIV, is now the third country globally, and second in sub-Saharan Africa, to exceed 95:95:95 targets. Results from the 5th Botswana HIV/AIDS Impact Survey revealed a national HIV prevalence of almost 21%; amongst that population, 95.1%, 98% and 97.9% knew their status, were on ART and were virally suppressed, respectively (4). This is against a global backdrop of 84% or people with HIV knowing their status, 87% of those being on ART and 90% of those on ART being virally suppressed (2). Botswana has also achieved excellent testing and ART coverage in pregnancy women: at antenatal registration in 2020, 99% of women were aware of their HIV status and 99% with HIV were on ART (5). This incredible progress has contributed to great success in reducing vertical transmission rates in the country.

HIV & STI prophylaxis

HIV pre-exposure prophylaxis

HIV pre-exposure prophylaxis (PrEP) has been available in the United States (US) for a decade, but uptake has been slow. In a prospective cohort of 1,313 trans women in Eastern and Southern US states taking surveys and oral HIV tests every 3-6 months over a 2–4-year period, HIV incidence was high (4.8 per 1,000 person years overall), particularly in black trans women (15.9 per 1,000 person years), highlighting missed opportunities to deliver HIV prevention (6).

Higher incidence in some ethnic groups is not surprising considering the inequity of PrEP access in the US. PrEP use in different US regions was measured using PrEP-to-Need Ratio (PnR) as a marker of PrEP equity, as opposed to just equality, by dividing the number of PrEP users by the number of new HIV diagnoses (7). Race/ethnicity data was available from commercial pharmacy

datasets for over a third of PrEP users (around 125,000 people on PrEP). Among this sample, PrEP use increased between 2020 and 2021 for all groups in all regions but not equitably with PnRs better for White and worse for Black people with the difference increasing over time. The absolute difference was greatest in the Northeast region in 2021, thanks to a marked rise in PnR amongst white people and a near plateau in Black and Hispanic populations. The US South lagged behind all other regions but exhibited the same pattern of highest PnR in White people with much lower PnR in Hispanic populations, then Black populations.

A choice of PrEP methods is important to maximise PrEP coverage and on the day the conference opened, ViiV Healthcare and the Medicine Patent Pool (MPP) announced a voluntary licensing agreement to expand access to long-acting injectable cabotegravir (LA-CAB) for PrEP (8). The agreement allows selected generic manufacturers to supply LA-CAB in 90 low-income countries, though each country will need to achieve regulatory approval first. Whilst this is undoubtedly great news, one protest during the MPP session focused on the fact that LA-CAB would remain out of reach for countries not considered low-income enough to benefit from this scheme. On the same day, WHO released their guidelines on LA-CAB PrEP (9). WHO takes a more pragmatic approach when it comes to HIV testing on PrEP, advising that this should be determined based on local resources and existing practice. In contrast, the CDC PrEP guidelines, which were the first to recommend LA-CAB, advise 2-monthly HIV testing including viral load, a test out of reach for many (10).

As for new data on LA-CAB PrEP, the conference saw an updated analysis of the HIV Prevention Trials Network (HPTN) 084 study, a randomised trial of intramuscular (IM) CAB versus daily oral tenofovir-disoproxil/emtricitabine in cisgender women at high risk of HIV acquisition (11). This was the first trial to demonstrate that PrEP could be highly effective in women, following a series of disappointing oral PrEP trials demonstrating low efficacy driven by low adherence. Published data from HPTN 084 demonstrated significantly fewer new HIV infections in women receiving LA-CAB than those on oral PrEP (12) and the updated analysis reported on new infections since the trial was unblinded at the end of 2021. Of 23 HIV infections detected during the 12-month unblinded phase (20 in the oral arm, 3 on LA-CAB), 2 were determined to have occurred during that phase – one in each arm - and only a third of the people acquiring HIV in the LA-CAB arm had ever received an injection. HIV infections remained statistically significantly fewer on LA-CAB (HR 0.11, 95% CI 0.05-0.24) and there were no HIV acquisitions on LA-CAB in the context of on-time injections (12). Of note, pregnancy incidence was higher in both arms during the unblinded phase, highlighting the importance of monitoring LA-CAB safety outcomes in pregnancy.

Whether LA-CAB is a cost-effective PrEP option depends very much on cost, of course. An analysis based on HPTN 084 and HPTN 083 (a similar trial conducted in men who have sex with men and transgender women) concluded that the price per injection would need to be in the range of $8.99 and $14.21 (less than twice the cost of a 2-month supply of oral ART), depending on uptake and duration of use, to be cost-effective in South Africa (14).

Continuing the topic of pregnancy safety, a study in Kenya explored neurodevelopmental and growth outcomes beyond 24 months in children exposed to oral tenofovir/emtricitabine PrEP in utero (13). Reassuringly, among 472 mother-child pairs, prenatal exposure was not associated with adverse growth outcomes at 24 to 36 months, nor with developmental outcomes at 30 to 36 months, supporting the safety of this PrEP option to infants born to women on PrEP.

A discrete choice experiment in 5,982 US men who have sex with men tested hypothetical long-acting PrEP (LA-PrEP) scenarios. Participants were asked to choose between pairs of PrEP options with differing costs, side effect profiles, efficacy and requirements for time spent in clinic (15). In total, 21% had heard of LA-PrEP and given a hypothetical choice of only one option, 74% chose LA-PrEP, 16% daily oral PrEP and 10% neither. Participants were asked to choose the most important

attribute of PrEP to them, and the attributes were ranked. Efficacy was considered the most important attribute (55% of relative importance) followed by low out-of-pocket cost (25%); a short time in clinic and low risk of side effects were considered relatively unimportant (12% and 7%, respectively).

A common theme in discussions about long-acting technologies is the importance of combining or aligning HIV prevention with other interventions, such as contraception. A 3-monthly long-acting PrEP option would not only reduce visits, but it could align with 12-weekly depot contraception provision. CAB pharmacokinetics in women support investigation of 3-monthly dosing and some results of a trial exploring this were presented at the meeting. Unfortunately, the 3-monthly pharmacokinetic data was not presented but the safety and pharmacokinetics of thigh intramuscular and abdominal subcutaneous LA-CAB administration were similar to the safety and pharmacokinetic of gluteal intramuscular LA-CAB (16). Novel routes of administration could overcome some of the practical barriers to LA-CAB use.

Preventing HIV transmission through breastfeeding

Undetectable=Untransmittable is still not applicable to breastfeeding. Breastmilk viral load testing is not routine, meaning further data is required to best inform current approaches to support the growing number of people living with HIV who wish to breastfeed/chestfeed.

The Well Project, an organisation focused on information for parents with HIV, explored attitudes to different materials providing education about infant feeding (17). Resources, including a fact sheet, a webinar featuring women with HIV who chose to breastfeed, and live-streamed events, reached thousands of women. The authors concluded that there is a huge demand for accessible information about infant feeding and called for the voices of parents with HIV to be central to the development of educational materials that support people with HIV to make informed, uncoerced infant feeding decisions.

Sexually Transmitted Infection (STI) Prevention

One of the most eagerly anticipated trials of STI prevention was DoxyPEP, a randomised trial investigating the impact of single-dose doxycycline given within 72 hours of condomless sex on STI rates. MSM and transgender women in Seattle and San Francisco underwent STI screening 3-monthly and when symptomatic (18). Amongst the 544 participants, who were randomised 2:1 to doxycycline vs no doxycycline, overall chlamydia, gonorrhoea, and early syphilis rates were significantly lower in the antibiotic arm at 9.6% vs 29.5% (relative risk (RR) 0.33; 95% confidence interval (CI) 0.23- 0.47; $p<0.0001$) as were the rates of each individual STI. STI rates remained significantly lower in the PEP arm when the analysis was restricted to the 194 participants living with HIV at 11.7% vs 27.8% s (RR 0.42; 95% CI 0.25-0.75; $p=0.0014$). These results prompted the trial Data Safety Monitoring Committee to recommend early termination ofhe trial at the first interim review in May 2022 as it was deemed unethical to continue the trial. An important concern about any strategy like this is the risk of driving antimicrobial resistance, not just for the infections of concern, but other genital and non-genital pathogens. The rates of gonorrhoea tetracycline resistance increased from 20% to 40% during the trial (18); doxycycline is no longer used to treat gonorrhoea, but for other infections it an important antimicrobial option. This is of particular importance in the United Kingdom, where tetracycline resistant gonorrhoea isolates have climbed from 40.9% to 65.1% between 2016 and 2020 (19). Careful monitoring of resistance is critical if this strategy is rolled out, but early termination of DoxyPEP will likely limit the information we can garner about the broader impact on antimicrobial treatment options. The CDC highlighted this concern in their response to the DoxyPEP findings, stating “we look forward to seeing additional data….to evaluate the potential individual and public health risks of doxy-PEP. For example… the change in doxycycline resistance in other common bacteria…. including staph.” (20).

HIV Treatment

The trial that generated most discussion was ALLIANCE, a randomised comparison of first line bictegravir/tenofovir-AF/emtricitabine (BFTAF) fixed dose combination and tenofovir-DF/emtricitabine plus dolutegravir (TDF/FTC+DTG) in people with HIV and chronic Hepatitis B (HBV) (21). A total of 243 people, most male, were recruited. Around 30% had a baseline HIV viral load above 100,000 copies/mL and 40% had a CD4 less than 200 cells/mm^3. 76-80% were HBV e-antigen (eAg) positive and baseline HBV-DNA was about 8log IU/mL. There was no significant difference in week 48 outcomes for HIV endpoints with high and similar proportions virally suppressed in both arms. However, HBV endpoints favoured BFTAF with higher rates of HBV-DNA suppression to less than 29 copies IU/mL, ALT normalisation and eAg loss. A very small proportion experienced surface antigen (sAg loss but this was also higher in the BFTAF arm (8% vs 3%, difference not statistically significant) (21). Of note, the HBV-DNA decay curves looked almost identical in the two arms suggesting that the slightly higher HBV-DNA on the TDF arm may be responsible for the differences in week 48 suppression and that with longer follow-up these differences could disappear. It is certainly, in our opinion, too early to conclude that BFTAF should be the preferred regimen, although anecdotally that appears to be a conclusion some have already drawn.

Very little new information was presented on injectable ART, but we will be watching the longer-term results of one trial with close interest. A pilot study of injectable CAB/rilpivirine (LA-CAB/RPV) San Francisco has included people not on ART with a median CD4 of 99 cells/mm3 and viral load of 50,000 copies/mL; 1 of the 15 has the N155H integrase mutation (22). Follow-up is limited but all experience prompt virological response and there had been no cases of treatment failure or resistance at the time of presentation. Registrational trials of LA-CAB/RPV, and consequently the product license, were restricted to people with no resistance and stable viral suppression. Therefore, we will depend on implementation projects and reports of real-world experience to explore this regimen in people fall outside these stringent criteria. LA-CAB/RPV could offer clear advantages for people who struggle sufficiently with oral ART that they cannot maintain an undetectable viral load.

In terms of ART choice in pregnancy, the dolutegravir (DTG) story has been a complex one. It was at the same conference 4 years ago that women protested the decision of some national guidelines to limit use of DTG in women of child-bearing age. This was driven by the Tsepamo cohort findings of a possibly higher risk of neural tube defects (NTDs) in infants born to women on DTG at conception (23). The concern that the finding of the initial analysis may have been driven by chance is supported progressive closure of the gap between NTD rates amongst women exposed to DTG at conception compared to those in women on efavirenz (EFV), other non-DTG ART or in HIV-negative women over time. This emphasises that caution is required when interpreting relative differences based on small numbers of outcomes. The cohort analysis is updated annually, and the data presented at this meeting included exposures up to March 2022. For the first time the confidence intervals for the NTD rate on DTG compared to all other groups, including HIV-negative women, cross zero so are no longer statistically significant (24). Earlier analyses, where the NTD prevalence difference was statistically significant, did not account for the relative benefits of DTG over EFV, the only reasonable alternative in many parts of the world, such as better viral suppression and lower risk of vertical and sexual transmission. With this latest analysis we can say, at last, that the persistent numerical difference in NTD rates is very small and DTG is as safe as other recommended ART regimens in pregnancy.

Summary

As countries like Botswana demonstrate that UNAIDS goals are not just achievable but can be surpassed. However, data from other countries in Africa showing very high rates of late HIV diagnosis highlights that timely testing is critical.

HIV testing is a gateway to accessing HIV prevention, including PrEP, but widening inequities in the US highlight the need to improve PrEP offer and uptake to the ethnic groups where HIV incidence is highest. Long-acting PrEP may be one route to improving PrEP access but it is unlikely to be cost-effective in some populations and more data on safety in pregnancy is required. We may soon be entering a new era of STI prevention following the early termination of the DoxyPEP trial, but the benefits in terms of incidence of chlamydia, gonorrhoea and early syphilis must be balanced against the risk of antimicrobial resistance limiting treatment options for other infections.

In terms of HIV treatment, longer-term follow-up of ALLIANCE is required before we can conclude that TAF should be preferred over TDF for people living with HIV and HBV. Longer-term outcomes are also critical before we can recommend the use of LA-CAB/RPV beyond people with stable viral suppression.

As most research is conducted in high-income countries, global calls sounded throughout AIDS 2022 for research to be conducted in low- and middle-income nations. As data on emerging therapies, technologies and behaviours are reported, community organisations continue to lobby for access to affordable drugs, and a rights-based approach to the future HIV response. May the loud community voices at AIDS 2022 shape the research presented at all conferences with a focus on HIV prevention and care.

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