IAS 2015 report: What clinical research was particularly relevant to young women living with HIV?

Antiretroviral therapy

The biggest news of the conference was the presentation of the results of the START trial, which is important for all people living with HIV. In this randomised controlled trial, HIV-positive adults naïve to treatment with a high CD4 count (above 500 cells/µL) were randomised to either immediate or deferred combination antiretroviral therapy (ART). The deferred group were monitored and initiated on treatment when their CD4 count fell to around 350 cells/µL (or to the development of a condition which necessitated initiation of ART). The trial population consisted of 4,685 people from around the world in high-, middle- and low-income countries; around 30% of participants were women.

The trial was stopped early by the Data and Safety Monitoring Board in May 2015 when it became clear that the rate of AIDS- and non-AIDS-related illnesses was significantly lower in the immediate-start arm. The analysis presented at the conference (and published the same day in the New England Journal of Medicine [1]) showed that people in the immediate-start arm had a 57% relative risk reduction in serious AIDS and non-AIDS events, compared to the delayed-start arm. The difference between the treatment arms was sustained when accounting for demographic and clinical variables, including age, gender, ethnicity, region, CVD risk and CD4 cell count. The results of the trial have important implications for all HIV-positive people not yet on treatment; an update of the BHIVA UK treatment guidelines recommending removing the CD4 cell count threshold for treatment is currently out for consultation.

The results of a Phase 3B study to evaluate the safety, efficacy and tolerability of a regimen containing elvitegravir/cobicistat/emtricitabine/tenofovir single-tablet regimen compared to a regimen of ritonavir-boosted atazanavir plus tenofovir/emtricitabine in adult women naïve to ART (the WAVES study) were presented at the conference [2]. At 48 weeks post initiation, 10% of women in the Stribild arm had dropped out and 16% in the atazanavir arm. 87% of women randomised to Stribild and 81% of women taking atazanavir achieved a viral load of less than 50 copies/mL at 48 weeks, establishing the 48-week virological superiority of Stribild in this population. When the analysis was restricted to women with a baseline viral load above 100,000 copies/mL, 90% of women in the Stribild arm and 78% of the women in the atazanavir arm achieved an undetectable viral load. These results add to the existing body of evidence that elvitegravir-based regimens have high efficacy and tolerability, with few side effects. Women are generally under-represented in HIV clinical trials and, as the authors point out, this means that these results also show that it is feasible to recruit, enrol and retain women in a large multinational clinical trial.

Adolescents living with HIV are a vulnerable and often under-served group, with poorer retention in care and treatment outcomes [3]. Many of the estimated 2 million adolescents living with HIV in the world were perinatally infected, meaning they often have had a long duration of infection, and therefore treatment, treatment interruptions, and virological failure with accumulated resistance. In addition, the physiological changes of adolescent maturation may affect drug pharmacokinetics [4]. Therefore, clinical trials specifically looking at this group are required. A small Phase II trial looking at the safety and efficacy of a rilpivirine-based regimen in 36 adolescents reported that 72% of participants achieved an undetectable viral load by week 48, and this was 79% in those with a

baseline viral load of less than 100,000 copies/mL. The safety profile and pharmacokinetics of the rilpivirine-based regimen was similar to that already reported in adult patients.

Adolescents with perinatal HIV are frequently already very treatment-experienced, and require long duration of ART after acquisition of HIV at a young age. In addition, they are on ART during key phases of growth and development, so research which investigates potential long-term toxicities of ART and strategies to avoid or minimise them are especially important in young people. Gaur *et al* reported the results of two single-arm open-label trials of elvitegravir-containing regimens, one containing tenofovir disoproxil fumarate (TDF), and the other containing tenofovir alafenamide (TAF), and compared 24-week safety data in 50 and 33 adolescents respectively [5]. TAF is a novel prodrug of tenofovir diphosphate which results in higher intracellular levels of tenofovir diphosphate and lower plasma levels, meaning it can be dosed at a much lower level than TDF. The incidence of proteinuria was lower in the TAF arm, and the spine bone mineral density at week 24 was higher, although the clinical significance of these findings is uncertain.

Co-morbidities

At the preceding International Workshop on HIV Paediatrics, Le Prevost *et al* from MRC CTU reported on anxiety and depression in young people with perinatal HIV and their HIV-negative siblings in the AALPHI study [6]. They analysed baseline data from a cohort of 290 adolescents aged 13–21 years living with perinatal HIV, and 99 HIV-negative controls (who were over 60% female overall) and found that having perinatal HIV was not associated with anxiety or depression scores, but that the death of both parents was associated with the higher anxiety scores. Higher self-esteem and quality of life was associated with lower anxiety scores. They suggested that although young people living with HIV do express feelings of anxiety and depression, levels were similar to the HIV-negative controls and the wider UK population. Questions from the audience included whether the tools used to measure anxiety and depression scores had been validated in people of Black African ethnicity, since 72% of the subjects in the study were Black African.

A small study presented by Sudjaritruk *et al* looked at the prevalence and associated factors of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis among perinatally HIV-infected adolescents in Thailand and Indonesia [7]. They included 51 young people aged 10 to 25 years with virologically supressed HIV, who had a history of transaminitis in the past 12 months, and these cases were compared to matched HIV-negative controls with normal liver enzymes. They excluded people with a history of hepatitis B or C infection or significant alcohol consumption. The prevalence of NAFLD was 18.6% and similar in both groups, but they found a higher prevalence of severe NAFLD and significant liver fibrosis in the HIV-positive group. They looked for predictors of NAFLD or fibrosis, but obesity, CD4 cell count prior to ART initiation, type and duration of ART were not associated with the presence of disease.

Reproductive health

Some results of the ELLA study were presented in a poster by van Wyk *et al* [8]. This was a cross-sectional survey which examined barriers to care affecting women living with HIV, and here they presented results on reproductive choices of nearly 2,000 HIV-positive women aged above 18 years

who had been enrolled from China, Central and Eastern Europe (CEE), Latin America (LA) and Western Europe and Canada (WEC). The mean age of these women was 40 years, 70% had had at least one live birth, and 61% were unwilling to have more children. Over 50% were living with a partner, and nearly 50% of these partners were sero-discordant. Despite this, between 20% (LA) and 27% (CEE) were using no form of contraception and this was 16% in sero-discordant couples. The most common contraceptive method used was male condoms (47–63%), 7% (China) to 20% (LA) were using abstinence, 18% had been surgically sterilised, and 11% were using an intrauterine device. Male condom use decreased with advancing age. Sero-discordant couples were more likely to be using any form of birth control, and more likely to use male condoms. The authors commented that although there was significant geographic variability in birth control methods, the fact that only half reported use of barrier protection, and that use decreased with advancing age meant that renewed efforts to educate women living with HIV regarding use of barrier methods to decrease HIV transmission should be considered. It would be interesting to know more about the age distribution of these women, since the mean age given is quite high and the authors do not give an upper age limit for participation in the study. It seems probable that the perceived risk of unplanned pregnancy in this population may be low given the high average age, and that women are less likely to use birth control if they perceive a low risk of unplanned pregnancy and are in a sero-concordant relationship.

Pyra *et al* presented the combined results of three longitudinal studies looking at the effectiveness of contraception in HIV-positive women on antiretroviral therapy living in Africa [9]. Over 5,000 women were followed up for a median of 1.8 years, and 41% of these women used injectable contraceptives (primarily DMPA), 15% oral contraceptive pill, 9% implant and 47% never used hormonal contraception. 23% of the women were on nevirapine and 5% were using efavirenz. Use of implants reduced the risk of pregnancy by more than 90%, both among women on ART (aHR 0.06) and not on ART (aHR 0.05). Injectables also reduced pregnancy risk, as did oral contraceptive pill, and there was no evidence that being on ART diminished contraceptive effectiveness. However, conclusions could not be drawn about individual ART agents owing to the small size of these groups. This data is reassuring and underlines the high efficacy of implants in preventing unintended pregnancies, even in women on ART. Unfortunately, access to implants is often restricted in resource-poor settings. Providing HIV-positive women with effective contraception to prevent unintended pregnancies is one of the pillars of PMTCT, and is essential in the current drive to eliminate new paediatric HIV infections worldwide.

Pregnancy and preventing mother-to-child transmission

In the UK, raltegravir is recommended to be part of the ART regimen used if the woman has presented to care late in pregnancy and rapid viral load decay is necessary to achieve suppression by delivery. Various cases have been reported in which this approach has been successful, but there is currently minimal evidence on the safety of raltegravir use in pregnancy in terms of short- and long-term infant outcomes in those exposed *in utero*. Kakkar *et al* presented a case series of 14 mother-infant pairs where the mother had taken raltegravir at standard dosing during the third trimester of pregnancy; there were no mother-to-child transmissions in this group, and no problems in the infants, who were followed up for a median of around 2 years [10]. This case series adds to the small

evidence base that we have on the use of raltegravir in pregnancy, but was not large enough to draw any conclusions about the safety or efficacy of raltegravir use in pregnancy, which requires large-scale surveillance.

A large cross-sectional survey of 2,521 pregnant women attending antenatal clinics in Kenya was presented by Ronen *et al* [11]. 13% of these women were adolescents, who were less likely to have above primary education, less likely to have intended the pregnancy, and less likely to have a current partner. Adolescents were also less likely to attend four or more antenatal visits. This effect remained significant when adjusting for education, parity, pregnancy intention and HIV status. 96% of women attending at least one antenatal visit were tested for HIV, with no difference between adolescents and adults. HIV-positive adolescents were less likely to use antiretroviral therapy during pregnancy than HIV-positive adults. Clearly, adolescents in this setting are marginalised and face additional barriers to accessing necessary antenatal care. The authors call for further research on the barriers that these young women face, and programmatic intervention to improve uptake and retention of this vulnerable population in the PMTCT cascade.

References

1 The INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015;:150720091517005. doi:10.1056/NEJMoa1506816

2 Mark Mascolini. Stribild Superior to Boosted Atazanavir in Treatment-Naive Women. Natl. AIDS Treat. Advocacy Proj. 2015.http://www.natap.org/2015/IAS/IAS_06.htm (accessed 29 Jul2015).

3 Sohn AH, Hazra R. The changing epidemiology of the global paediatric HIV epidemic: keeping track of perinatally HIV-infected adolescents. *J Int AIDS Soc* 2013;**16**. doi:10.7448/IAS.16.1.18555

4 National Institute of Health. Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents | Pediatric ARV Guidelines. AIDSinfo. https://aidsinfo.nih.gov/ (accessed 29 Jul2015).

5 H Kizito, A Gaur, W Prasitsuebsai, *et al.* Changes in renal laboratory parameters and bone mineral density in treatment-naive HIV-1 infected adolescents initiating therapy with INSTI-based single-tablet regimens containing tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF). Vancouver, Canada: 2015.

6 M le Prevost, D Melvin, A Nunn, *et al.* Anxiety and depression in young people with perinatal HIV and their HIV-negative siblings. Vancouver, Canada: 2015.

7 T Sudjaritruk, T Bunupuradah, L Aurpibul, *et al.* Prevalence and associated factors of nonalcoholic fatty liver disease and liver fibrosis among perinatally HIV-infected Asian adolescents. Vancouver, Canada: 2015.

8 R Kulasegaram, A D'Arminio Monforte, J Valdez Madruga, *et al.* Reproductive choices of women with HIV-1 Infection: the ELLA study. Vancouver, Canada: 2015. http://pag.ias2015.org/Search/Index (accessed 4 Aug2015).

9 M Pyra, R Heffron, NR Mugo, *et al.* Effectiveness of contraception for HIV-infected women using antiretroviral therapy: combined data from 3 longitudinal studies. Vancouver, Canada: 2015.

10 MJ Trahan, V Lamarre, ME Metras, *et al.* Raltegravir for the prevention of mother-to-child transmission of HIV. Vancouver, Canada: 2015.

11 K Ronen, C Mcgrath, A Langat, *et al.* Lower ANC attendance and PMTCT uptake in adolescent versus adult pregnant women in Kenya. Vancouver, Canada: 2015.