Highlights from the 9th International Workshop on Pediatrics 21–22 July 2017, Paris France

The *9th International Workshop on Pediatrics* was held in Paris, France on the 21–22 July, 2017. It was co-chaired by Lynne Mofenson (EGPAF, USA), Albert Faye (University Paris Diderot, Paris, France) and Valériane Leroy (INSERM, France). Over 300 participants attended the workshop. The abstracts included 20 oral presentations, 87 posters and 45 abstract book-only abstracts. (Workshop materials such as abstracts and presentations can be found at: www.infectiousdiseasesonline.com).

Session 1: Pediatric treatment and management

Pediatric HIV in Eastern Europe, PMCT in an urban area in the US, digital technology and adherence, and a single-tablet regimen for the under 12s

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Natella Rakhmanina gave an overview of the current status of the HIV epidemic in Eastern Europe. Independent of varying definitions of the Eastern European region, most of the HIV epidemic is concentrated in Russia and Ukraine, accounting for the estimated 85–90% of people living with HIV in the region [1,2] (Figure 1). Throughout the last decade, the epidemic has continued to rise with Eastern Europe mostly contributing to the unprecedented high number of 153,403 new HIV infections within European Region in 2016 [1,2]. The three biggest challenges facing the region are: the increasing number of heterosexual transmissions in women of childbearing age, which overtook injecting drug use transmissions in males; the high number of people living with HIV who remain undiagnosed; and low antiretroviral treatment (ART) coverage among people living with HIV.

Despite the overall growth of HIV epidemic during last decade, Eastern Europe has witnessed a steady decline in the rates of mother-to-child transmission (MTCT) of HIV, with Belarus and Armenia reaching the WHO elimination target in 2016 of fewer than 50 HIV infections per 100,000 live births. Even in Russia and Ukraine, MTCT national rates have remained below 2% [1-3]. With the current rise in heterosexual transmission in the region, however, women of childbearing age are progressively making up an increasing proportion of people living with HIV. Maintaining focus on targeted repeat HIV testing and prevention of MTCT, including implementation of PrEP in pregnancy and the postpartum period for women with high-risk partners, is required to avert the potential rise in MTCT in Eastern Europe.

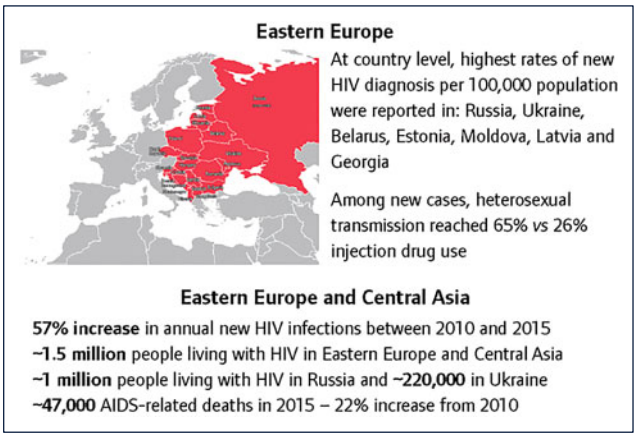

Figure 1. HIV in Eastern Europe, 2015

Adolescents and youths aged 15–24 years accounted for less than 10% of all new cases in Eastern Europe in 2015; however, the actual epidemic within this age cohort is most likely to be underestimated [2]. The young people of the region have multiple risk factors for HIV including a lower age for becoming sexually active, exposure to alcohol and drugs, gender inequality and gender-based violence, labour migration, displacement, human trafficking, marginalisation and sexual exploitation [1,2,4]. Among those living with HIV, perinatally infected adolescents and youth frequently lack family support and have history of institutional care placement [4]. Horizontally infected youth are diagnosed late and frequently face substance abuse with limited harm reduction and treatment options [4]. The scope of the epidemic amongst young men who have sex with men (MSM) remains largely unknown except in a few countries [1,2,4]. Finally, limited data on engagement in care and transition suggest high rates of loss to follow up [4]. Overall, better data on adolescents living with HIV including marginalised and young MSM populations are urgently needed in Eastern Europe.

In a poster presentation, Ellenberger *et al.* evaluated approaches to and outcomes of PMTCT during 2013–2015 in a high HIV prevalence metropolitan area in the USA [5]. In a retrospective cohort analysis of 279 HIV-exposed infants (HEIs), low MTCT risk was observed among the majority (85%). Despite low risk and contrary to the national neonatal prophylaxis guidelines, a significantly large proportion of mothers (72%) received intravenous zidovudine (ZDV) and more than half (57%) had a Caesarean section. Evaluation of indications for Caesarean section is ongoing to identify whether it was based on MTCT risk assessment or obstetric/neonatal factors. Among high-risk HEIs with a high risk for MTCT, a significant proportion (40%) of US-born infants received postpartum mono-prophylaxis with ZDV, while 58% received dual or triple antiretroviral drug combinations. No perinatal transmissions occurred within the studied cohort.

HIV-positive youth are known to be at high risk for poor adherence to ART. Digital game-based interventions are promising, especially among adolescents. In this poster presentation, Griffith *et al.* aimed to examine the uptake of interactive smartphone-based games interlinked with a medication-monitoring device (Wisepill dispenser) among a cohort of 24 (mean age=18 years; 12 males, 12 females) HIV-infected adolescents and young adults (AYA) on ART [5]. Participants opened their Wisepill dispensers only 25% of the time based on the prescribed ART frequency of once per day (407 actual/1607 prescribed openings). Although a real-time, electronic ART adherence monitoring system interlinked with smartphone gaming was clearly technically feasible, the authors reported low uptake of this technology among the cohort of HIV-infected AYAs with documented suboptimal ART adherence. Data from ongoing exit surveys will be used to modify gaming and adherence monitoring design.

Currently, no once-daily single-tablet regimen (STR) is approved for use in HIV-infected children under 12 years of age [6]. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF; E/C/F/TAF) is a once-daily integrase inhibitor (INSTI)-based STR approved for use in adults and

adolescents aged 12 years and over and weighing at least 35 kg. In a poster presentation, Rakhmanina *et al.* reported safety and efficacy data for using E/C/F/TAF in younger, virologically suppressed children (6–<12 years of age and weighing ≥25 kg) through week 48. In 23 (median age 10 years, median weight 31 kg, 61% female, 78% black) HIV-infected children weighing at least 25 kg, the currently available formulation of E/C/F/TAF was well tolerated and safe, reflected by sustained virological suppression and a persistent favourable renal and bone safety profile out to week 48. These findings support the safety and efficacy of E/C/F/TAF as the first once-daily INSTI-based STR in children weighing ≥25 kg.

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Virological dynamics and very early antiretroviral treatment

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Renate Strehau presented data from the Leopard study in which 75 perinatally HIV-infected children started ART either before 48 hours (group 1, *n*=33), from 48 hours to 7 days (group 2, *n*=22), and after 8 days of life (group 3, *n*=20) [1]. Initiation of very early ART in primary HIV infection may alter the pathogenesis of HIV and a rapid decline in viral load is postulated as a first step by which early treatment may lead to remission. In this study, virological suppression rates to below 20 copies/mL at 12 months post-ART were 63.3% in group 1, 63.6% in group 2 and 45.0% in group 3. Overall, 40%, 36.4% and 30% had sustained suppression by 12 months in groups 1, 2 and 3, respectively. Time to suppression was slightly better in infants with very early treatment (before 48 hours). No one initiating ART after 8 days had a negative HIV-DNA PCR, whereas 16.7% and 13.6% of groups 1 and 2 had negative diagnostic HIV-DNA PCR, respectively. There were subtle differences between those treated <48 h after birth and those treated slightly later. Additionally, more sensitive virological markers may be required to see whether very early ART influences the possibility for viral remission.

Victoria Iyun presented data from the South African International Epidemiology Databases to Evaluate AIDS (IeDEA) cohorts, looking at the changes in characteristics and outcomes for infants initiating ART [2]. Although changes in prevention, testing and treatment guidelines have led to infants initiating ART earlier and with higher CD4 cell counts, a significant proportion still start with advanced disease (39% at WHO stage advanced/severe in 2013–2016 compared to 84% in 2006–2009). Additionally, estimates of mortality at 6 months following initiation of ART (5% in 2013–2016 *vs* 10% in 2006–2009) and loss to follow up (14% in 2013–2016) remain unacceptably high. Innovative approaches are required to ensure that HIV-infected infants in routine care setting achieve optimal treatment outcomes

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Mortality, growth and virological failure

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Valériane Leroy reported data from over 28,000 youths from 28 countries in the International Epidemiology Databases to Evaluate AIDS (IeDEA) network, comparing mortality and clinical events before and after ART initiation [1]. The study highlighted the ongoing need to ensure rapid diagnosis and early access to treatment in those aged <2 years. Mortality decreased in all children aged under 10 years (but not in those aged 10–24 years) from 2.48 (95% CI 2.28–2.77)/100 person years pre-ART to 1.22 (1.18–1.30)/100 person years post ART. However, mortality was substantially higher both before and after ART initiation in children under 2 years old (8.60, 95% CI 7.99–9.26) decreasing to 5.60 (95% CI 5.24–5.97)/100 person years, respectively. Similarly, the incidence of both World Health Organization (WHO) HIV disease stages 3 and 4 events reduced after ART initiation in all age groups, but was highest in both time periods in those under 2 years old.

Julie Jesson also presented preliminary data from the IeDEA network describing growth and stunting in HIV-infected adolescents aged 10–19 years [2]. By 10 years old, 38% were stunted with the rate rising to 45% by age 15 years. Mean height-for-age z-scores were similar in 10-year-old males and females, but by 19 years of age, it was higher in females, which may be due to growth spurts occurring earlier in females. In both sexes, the rate of growth during the adolescent growth spurt was less rapid than would be expected in an uninfected population. Therefore, being able to identify when the growth spurt starts may aid in the development of nutritional interventions targeted at adolescents to maximise potential growth during adolescence.

Incidence of virological failure in children and adolescents living in Europe and Thailand in the EPPICC cohort was described by Ruth Goodall [3]. In 2636 children who initiated ART at a median age of 6 years, 31% (95% CI 29–33) experienced virological failure by 5 years after ART initiation. Risk of failure varied by age and was highest in infants and adolescents, potentially due to dosing difficulties in infants and poor adherence in adolescents, highlighting the need to ensure adequate support in the clinic for these groups. A lower risk of failure was also reported in those taking an abacavir-containing regimen but there was an increased risk associated with nevirapine when compared to efavirenz- or boosted PI-based regimens.

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Debate: should integrase inhibitors (INI) be first-line for children

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Alfred Faye argued in favour of using INI as first-line therapy in children, based on the efficacy, toxicity profile, availability and palatability of INI, along with low risk of drug–drug interactions. INI are efficacious in achieving viral suppression with a low dose and, in a meta-analysis of adult data, have greater efficacy than NRTI and PI, with similar efficacy to NNRTI. Dolutegravir remains effective even in ART-experienced patients due to its favourable resistance profile [1]. Regarding toxicity profile, the FLAMINGO trial in adults [2] showed a higher relative risk of discontinuation for darunavir compared to dolutegravir; the primary reasons were gastrointestinal and lipid effects [3]. With regard to formulation and availability, raltegravir is approved for use from 4 weeks of age following data from P1066 and is available as a paediatric suspension, low-dose chewable tab or dispersible tab allowing low doses. With regard to potential drug interactions, dolutegravir has fewer interactions than PIs with commonly co-administered drugs, particularly rifampicin [3,4]. Finally, the US 2017 guidelines recommend raltegravir from 2 to 6 years and dolutegravir from 6 years while the WHO 2016 guidelines do include integrase inhibitors as a first-line option for adolescents where available.

Victor Musiime argued against using INI as first-line regimen in children, citing very limited data in ART-naïve children; most data were from naïve adolescents and ART-experienced children. Current WHO guidelines recommend dolutegravir only for adolescents. Two large paediatric trials are underway and will be available soon: P1093 available May 2018 and ODYSSEY in2019. Since both PI and NNRTI efficacy is excellent with low discontinuation rates [P1060 and CHAPAS-3], there is no urgency to find a replacement drug. The cost of dolutegravir is substantially higher than competing drugs. Dolutegravir did not show cost-effectiveness compared to EFV at branded (i.e. non-generic) prices [5]. Lower-middle income countries (LMIC) have more urgent competing priorities for their health spend, namely increasing testing, ART initiation and viral load suppression rates. INI are not without side-effects, showing a 5–15% discontinuation rate largely due to neuropsychiatric events and increased suicide risk [6]. In addition, the rate of adverse events is increased when combined with abacavir, a key backbone first-line drug for children [7]. Musiime contested that the resistance profile is not a concern, citing a study that found new mutations detectable by week 4 and clinically significant resistance by week 17 [1]. Since pharmacovigilance in resource-limited settings is very limited, blanket implementation of integrase inhibitors as first-line in children may hold substantial risk in LMIC. Musiime concluded that there is currently insufficient evidence to recommend INI for first-line regimen in children and thus a guideline change would be premature.

From the audience, Lynne Mofenson contested Dr Faye's assertion that existing adult RCT data is sufficient, citing at least two clinical trials where paediatric and adult outcomes differed, including PENPACT and the double-dose Kaletra trials. Polly Clayden from iBase pointed out that although current INI prices are high, there is a global push by UNITAID, CHAI and Viiv to reduce INI prices through generic manufacturing. Nandita Sugandhi pointed out that the raltegravir paediatric suspension is not user-friendly and the currently available dolutegravir tablet formulations require two different-sized tablets per dose, and this complexity would be a barrier to implementation in LMIC.

Ultimately, audience opinion remained split between the two arguments.

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Session 2: Models and comorbidities/coinfection

Using infant animal models to advance pediatric HIV prevention, vaccines and cure

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As part of the session on 'Models and Comorbidities/Coinfections', Ann Chahroudi presented an overview of the use of infant animal models to advance our understanding of HIV pathogenesis, prevention and cure [1]. This talk was meant to provide a bridge between clinical questions in paediatric HIV and the opportunities afforded by translational non-human primate models to approach these questions (Table 1). Chahroudi first reminded the group of the origin of HIV-1 and HIV-2 from simian immunodeficiency virus (SIV) strains that naturally infect non-human primate species in the wild as well as the SIVmac viruses that are used experimentally to infect rhesus macaques [2]. Like HIV-1 infection of humans, SIVmac infection of non-natural host rhesus macaques results in a pathogenic infection that leads to simian AIDS, with similar viral dynamics and vigorous but ineffective immune responses, key pathogenic events such as chronic immune activation, and the existence of a benign clinical outcome in a minority of infections that is associated with specific MHC alleles [3]. Importantly, the model of SIVmac infection of rhesus macaques permits exquisite experimental control, in terms of the timing, route and dose of infection with a defined virus inoculum, assured adherence to treatment regimens (including antiretroviral therapy), access to tissues via longitudinal biopsies and after elective necropsy (where brain and other typically non-accessed organs can be studied), and the ability to test novel interventions for both safety and efficacy.

Table 1. Use of infant non-human primates (NHP) for HIV/AIDS research priorities

Research priority	NHP model
Transmission	Breastfeeding infection model: • Postpartum SIV infection of dam • Oral SIV inoculation of infant *In utero*/intrapartum infection model: • SIV inoculation of amniotic fluid
Pathogenesis	Comparative model of pathogenic SIV infection in macaques and non-pathogenic SIV infection in natural hosts
Persistence/cure	SIV/SHIV-infected, ART-suppressed macaques • Test novel interventions • Investigate anatomical reservoirs
Prevention	Active and passive immunisation of macaques with SIV/SHIV challenge

SIV: simian immunodeficiency virus; SHIV: simian human immunodeficiency virus; ART: antiretroviral therapy.

The comparative models of pathogenic SIV infection in non-natural host rhesus macaques and non-pathogenic SIV infection of natural host non-human primate species (sooty mangabeys, African green monkeys, etc.) have provided many insights into the mechanisms of HIV transmission and pathogenesis. Work on CCR5 expression as a determinant of vertical transmission in infant rhesus macaques versus sooty mangabeys was described. The low level of CCR5 expression on CD4+ T cells in infant natural hosts, particularly in mucosal sites, is distinct from the high levels found in infant rhesus macaques and humans, and is hypothesised to be responsible for the restriction of vertical transmission in natural hosts [4,5].

In the area of prevention, Chahroudi highlighted the role infant rhesus macaques have played in testing paediatric HIV vaccines and passive immunisation with broadly neutralising antibodies (bNAbs). The induction of SIV-specific CD8+ T cell responses in blood and tissues following adenovirus vectored vaccines containing SIV gene inserts administered to neonatal macaques was described [6]. In addition, parallel testing of vaccine strategies in infant macaques using MVA vectors and HIV envelope protein are ongoing and are being utilised to guide development of a paediatric vaccine protocol within the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network (K. De Paris, unpublished data). Next, the use of bNAb as post-exposure and during breastfeeding exposure prophylaxis was considered. The IMPAACT P1112 trial is currently testing the bNAb VRC01 in each of these settings and initial work testing VRC01 in infant macaques provided useful pharmacokinetic data for this study [7]. Furthermore, repeated administration of a combination of two bNAbs (VRC07 and PGT-121) was recently demonstrated to clear infection in infant macaques exposed to simian-human immunodeficiency virus (SHIV) [7].

In closing, Chahroudi presented work from her laboratory in which SIV-infected, ART-suppressed infant rhesus macaques are used to characterise virus persistence in cellular and anatomical reservoirs. As mentioned, access to tissues such as the brain, lymph nodes and gastrointestinal tract that serve as crucial sites of persistent virus is a true advantage to the infant macaque model as these organs cannot be readily obtained from paediatric patients. In a related poster presentation, Rosyln Taylor *et al.* utilised a neonatal rhesus macaque model to investigate the earliest sites of infection following oral viral challenge (simulating breast milk transmission) [8]. In their study, neonatal macaques were orally exposed to a non-replicating reporter virus as well as a replication-competent SHIV four times per day and, at 53 and 96 hours after the first viral challenge, tissues were examined for evidence of infection. At 53 hours, viral infection was observed in the neck lymph nodes and upper gastrointestinal tract, including the oesophagus and stomach, with more widespread infection of the GI tract, oral mucosa, tonsils, spleen, and liver at the later time point. In summary, infant non-human primate models are particularly useful for studying PMTCT and HIV cure/remission approaches relevant to the paediatric population. These infant models serve as a highly translational system to test novel interventions that can then be formally evaluated in clinical trials.

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Disclosure

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Antiretroviral therapy has dramatically improved survival of children living with perinatally transmitted HIV. Together with improved ART access, disclosure of the child's HIV status has been identified as a necessary element of care; however, a lack of skills has been noted in both caregivers and health providers. Elijah Paintsil's study evaluated the impact of a structured intervention on the rate of care-giver disclosure in a study of 433 participants [1]. At 48 weeks, disclosure was 5.5 times more likely to occur in the intervention group than in the control group.

This study positively impacted HIV disclosure status for children in Ghana using a structured disclosure intervention. This intervention was also noted as being feasible from a cost-effectiveness point of view as well as being easy to scale up nationwide.

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Transition of care

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During the poster discussion, C Sethaputra described results from the Study of Transitioning Asian Youth (STAY), a pilot study of 83 young people aged 16–24 years transitioning from paediatric to adult care in Southeast Asia [1]. The study found that most felt prepared and ready for the transition to adult care, but over two-thirds still felt that they had to keep their status secret. This in turn may impact on social support with one-third feeling that there was no one in their life with whom they could share personal problems.

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Session 3: Prevention of mother-to-child transmission

Dolutegravir, raltegravir, tenofovir and efavirenz

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The use of antiretroviral drugs in the reducing MTCT has been one of the great successes of the ART era. There are, however, concerns around the possible effects of these drugs on the unborn fetus and an increase in the incidence of preterm births.

Integrase strand inhibitors are increasingly uses as part of the antiretroviral regimens for adults and adolescents. The use of the integrase inhibitor, raltegravir (RAL), as adjunctive therapy in the management of mothers who either present at a late gestation or who are not virally suppressed prior to delivery has not been fully explored. While placental transfer of another integrase inhibitor, dolutegravir (DTG) has been previously demonstrated, little is known about the safety outcomes related to its use during pregnancy.

Claire Thorne presented results from 101 pregnancies with exposure to DTG regimens on behalf of the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) [1]. Of 84 pregnancies with outcomes to date, there were 81 livebirths, one stillbirth, one spontaneous abortion and one induced abortion. Among the 80 singleton infants, 13.8% were delivered preterm and 18.7% were small for gestational age (SGA). Prevalence of congenital abnormalities was 4.9% (4/81, 95% CI 1.4–12.2). Although the small numbers preclude firm conclusions regarding DTG safety, these findings contribute to other studies presented at International AIDS Society (IAS) on DTG use from the Antiretroviral Pregnancy Registry and from the Tsepamo study in Botswana [2].

Thanyawee Puthanakit presented data on the outcomes of a strategy in Thailand of intensification of ART using RAL for HIV-infected pregnant women who presented after 32 weeks' gestation and/or are on ART have a high viral load (>1000 copies/mL) between 32 and 36 weeks' gestation [3]. In this cohort of 101 women the perinatal transmission rate was 2.7% with only two cases of HIV infection, one of which was probably an *in utero* transmission. Additionally, 78% of pregnant women achieved HIV RNA <1000 copies/mL by delivery. Although drug cost could be reduced in a large-scale national programme, in this pilot programme, it cost US$5000 to prevent one perinatal HIV infection using RAL. This study demonstrated the feasibility and effectiveness of a risk-based approach for prevention of MTCT with RAL intensification.

Jason Brophy reported on the association between tenofovir (TDF)-based ART and preterm delivery (PTD) [4]. The study compared the rate of PTD among women treated with TDF or other ART combinations using data from the Canadian Perinatal HIV Surveillance Program for the period 1997–2015. In this cohort of 2816 mother–infant pairs, 15.1% (501 pairs) were on a TDF-based ART. The overall rate of PTD was 16%, with a significantly higher rate in women treated with TDF versus not (19.4% *vs* 15.2%, P=0.022). Increased use of TDF over calendar time in general was also observed (from 0.77% in 2004 to 54.1% in 2015). TDF use, injecting drug use and elevated viral load were all associated with PTD in the multivariable analysis.

Data from the PROMISE study on hepatotoxicity in postpartum women initiating efavirenz (EFV)-containing ART, using liver enzyme elevation (LEE) to characterize the incidence, severity and predictors of EFV-induced hepatotoxicity was reported by Pat Flynn (St Jude Children's Research Hospital, Memphis, TN, USA) [5]. The study collected data on 3575 women of whom 2430 (68%) initiated EFV. Of these 2430, 180 had ≥grade 2 and 61 ≥grade 3 LEE. There were 13 deaths. More than 7% of postpartum women initiating EFV had a ≥grade 3 hepatotoxicity rate, with older age being the only other risk factor noted among this group. Monitoring for liver function abnormalities may prevent unnecessary deaths but research is needed to identify frequency and who is at highest risk for hepatotoxicity.

Ellen Chadwick presented data from an ongoing study (IMPAACT P1115) regarding the association of high grades (3/4) of asymptomatic haematological toxicity with very early initiation of ART (within the first 48 hours of life) among *in utero* HIV-infected infants [6]. High-risk HIV-exposed neonates were enrolled, divided in two cohorts (infected *in utero* (IN) *vs* uninfected *in utero* (UN)); both groups received three-drug regimens, and both initiated within 48 hours of birth. Data on 255 infants in 11 countries were collected between 2015 and 2017: 30 were IN and received ART for a median of 13.9 weeks, while 225 were UN and received a median of 1.2 weeks of cART. The haematological toxicity was more common in IN (13/30, 43%) vs. UN (16/225, 7%) infants. Amongst 13 IN infants with at least grade 2 haematological toxicity relating to ART, substituting abacavir or stavudine for zidovudine led to improvement. Early replacement of zidovudine with abacavir was suggested as a suitable strategy to avoid haematological adverse events in early treated infants.

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HIV-exposed uninfected infants and children

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Kate Powis (Harvard University) was invited to share her thoughts on the dilemma of HIV-exposed uninfected (HEU) children [1]. With expanding interventions to prevent HIV transmission from mothers to their children, approximately 1.25 million HEU children are born annually and are increasingly exposed to antiretroviral drugs *in utero* and during infancy. In high-HIV burden countries in southern Africa up to 25% of children are HEU. Dr Powis drew attention to three systematic reviews and meta-analyses on mortality in HEU compared to HIV unexposed (HU) children from 2016 demonstrating a 70–100% increased risk for mortality for HEU status [2-4]. HEU children start life more often preterm or small-for-gestational age, experience impaired length growth, higher incidence of pneumonia as well as a greater risk of pneumonia-associated treatment failure, and possibly subtle impairments in neurological development compared to HU children [5-11]. The aetiology of these health disparities is complex. With this evidence of elevated HEU child morbidity and mortality, the opportunities and challenges to establishing long-term surveillance of HEU child outcomes were detailed. With investment, existing national and global programmes for prevention of mother-to-child transmission, early infant diagnosis, child health and poverty eradication could be leveraged and synergies identified to avoid implementing a parallel surveillance program for HEU children in high HIV-burden countries.

Following this, Amy Slogrove (University of Cape Town and Stellenbosch University) presented an analysis of the population effect of HIV-exposure on mortality in HIV-uninfected infants in Botswana and South Africa [12]. Using published estimates of the relative risk for mortality in HEU compared to HU infants (relative risk (RR) 1.8; 95% CI 1.1–2.8) [3], she estimated that excess mortality in HEU infants accounts for 17% (range 3–31%) of all HIV-uninfected infant mortality in Botswana and 15% (range 2–29%) in South Africa. This excess HEU infant mortality is increasing the infant mortality rate by approximately five excess deaths per 1000 HIV-uninfected infants in both countries. According to the Thembisa combined HIV and demographic model for South Africa, the contribution of excess HEU infant mortality to all infant mortality in South Africa has increased from 1% in 1990 to 14% in 2015. At these rates, this excess HEU infant mortality threatens achievement of Sustainable Development Goal 3 (to ensure healthy lives and promote health and well-being for all at all ages).

Stanzi Le Roux (University of Cape Town) shared findings on the developmental outcomes of HEU infants in the context of universal maternal antiretroviral therapy [13]. Using the Bailey Scales of Infant and Toddler Development – 3rd Edition (BSID-III), cognitive, motor and expressive language development were assessed in a cohort of HEU and HU infants at 12 months of age, all breastfed and from a single peri-urban community in Cape Town, South Africa. A greater proportion of HEU compared to HU infants had cognitive (10% vs 5%, P=0.02) and motor (9% vs 4%, P=0.04) delay, but not expressive language (18% vs 14%, P=0.31) delay. Greater odds of cognitive delay in HEU infants persisted after adjusting for confounders (adjusted odds ratio [aOR] 2.32, 95% CI 1.10–5.08). Delay in motor development was substantially modified by preterm birth. Compared to term HU infants, term HEU infants had a similar odds of motor delay (aOR 1.21, 95% CI 0.47–3.11); however, preterm HU infants had an almost five-fold greater odds of motor delay (aOR 4.84; 95% CI 1.36–17.21) and preterm HEU infants had an almost 17-fold greater odds of motor delay (aOR 16.90; 95% CI 5.47–52.21). These findings indicate that even in the context of universal maternal ART and breastfeeding, HEU infants are at higher risk of cognitive and motor delays than HU infants, with preterm HEU infants being particularly vulnerable. The underlying processes driving these neurodevelopmental differences need detailed study to design screening and early intervention strategies to be incorporated in the lifelong care of HEU infants and children.

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Session 4: Adolescent HIV

The second generation, inequalities, adolescent friendly clinics and transition of care

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Jennifer Jao (Icahn School of Medicine at Mount Sinai, New York, NY, USA) opened this session with a talk entitled 'The second generation: pregnancy in women with perinatally acquired HIV' [1]. The first children who were perinatally infected with HIV were born in the mid-1980s and survivors are now of childbearing age. Since 2000, there have been steadily increasing rates of pregnancy

in this population; however, women in this group have been found to be less likely to discuss family planning with their healthcare providers and have higher rates of abnormal cervical cytology screening compared to their HIV non-infected counterparts. Lower rates of cervical cytology screening are also seen in sexually active adolescents with perinatally acquired HIV.

Pregnant women in this group have been found to have greater risk for immunosuppression, higher postpartum mortality rates and lower CD4 cell counts along with persistently higher viral loads than their counterparts with behaviourally acquired HIV pre-pregnancy, during pregnancy and also post-pregnancy. They have also been found to be more likely to have therapeutic terminations of pregnancy as well as being more likely to develop multiclass ARV resistance. Fortunately, this has not affected MTCT rates overall. Maternal perinatally acquired HIV has not been found to be associated with babies who are small for gestational age stillbirth in Europe and North America.

Some studies have shown that infants of women with perinatally acquired HIV experience lower weight for age Z-scores and higher rates of infectious disease-related hospitalisations although, overall, there is still a paucity of data on long-term outcomes.

Questions that remain to be answered are: how perinatally acquired HIV affects pregnancy and health outcomes in resource-limited settings such as in sub-Saharan Africa; what the long-term postpartum health of women with PHIV will be; and also what the long-term health of their children will be.

In the first oral abstract presentation for this session, Marcel Yotebieng (College of Public Health, Ohio State University, OH, USA) presented work on the inequality in outcomes for adolescents living with perinatally acquired HIV in sub-Saharan Africa (SSA) [2]. SSA is home to 80% of the 1.8 million adolescents living with HIV, who have a two to four times greater mortality hazard than their counterparts elsewhere globally. Progress in diagnostic and treatment interventions is not uniform across the continent, with younger adolescent AIDS-related deaths starting to decline in some countries, whereas these rates continue to rise in others. The primary objective of this study was to compare characteristics and outcomes (mortality, transfer out and loss to follow-up) of adolescents with perinatally acquired HIV (APH) by country income group (CIG) in SSA. The study pooled individual retrospective data from 12 cohort networks globally with data used for the SSA analysis taken from 25 countries represented by seven networks. Characteristics were compared by CIG at first visit, initiation of ART, age 10 years and last visit. Cumulative incidence for outcomes was calculated using competing risks analysis and mortality hazard ratios using Cox proportional hazard models. A total of 30,296 APH were studied with 75.7% from low-income countries (LICs), 4.6% from lower-middle income countries (LMICs) and 19.8% from upper-middle income countries (UMICs). Approximately two-thirds of children were born in or after the year 2000 and median age of first visits ranged from 6.6 years in UMICs to 7.3 in LICs, age of ART initiation from 7.3 years in UMICs to 8.1 years in LICs, and for last visits 12.4 years in UMICs to 12.0 years in LICs. The median CD4 cell count at ART start was approximately 300 cells/mm^3 with the largest changes in mean CD4 cell count seen between starting ART and last visits in LMICs (463 cells/mm^3) and the smallest in LICs (295 cells/mm^3). Improvements in height were seen in both LICs and UMICs but not LMICs. UMICs saw the highest median improvement of WHO height-for-age-z-scores of 0.43. Mortality rates were lowest in UMICs at 1.1%, 3.5% in LICs and highest in LMICs at 3.9%. However, it must be noted that the loss to follow-up rates were highest at 14.1% in the UMIC group. APHs living in LICs and LMICs had hazard ratios in survival analysis data approximately three times higher than that of their peers in UMICs.

The current generation of APHs in SSA have largely experienced improvement in immune status and growth despite starting ART at more advanced ages. However, it must be mentioned that in this study, even when receiving ART, inferior growth parameters and higher mortality rates were seen in LICs and LMICs compared to UMICs in SSA. These differences could be explained by differential mortality ascertainment and the large spectrum of levels of care (from routine care centres to centres of excellence) rather than inequalities that could be explained by CIG classification itself.

In the future, more detailed growth analyses are planned, as well as a more studies to increase understanding for the reasons for the lack of retention in care of APH, and to better compare and interpret estimates of mortality. The nature of new and ongoing APH cohorts will continue to be followed.

S Teeraananchai (HIV-NAT Research Collaboration and Kirby Institute, Sydney, Australia) presented work on the attrition and treatment outcomes among adolescents and youths with perinatally and behaviourally acquired HIV [3]. Following the success of pilot programmes in Thailand, the Thai National AIDS programme was expanded into the Universal Health Coverage Programme in 2006 and managed by the National Health Security Office (NHSO). On this programme, free first- and second-line regimens are available as well as free 6-monthly testing for CD4 cell counts and viral loads. Since 2007, there has been a decreasing trend of children who start ART between the ages of 10 and 14, and instead, an increasing trend of those starting ART between the ages of 15 and 24, which may be explained by the success of PMTCT programmes as well as the increase in behaviourally acquired HIV. For the purposes of this study, those starting ART at ages 10–14 were classified as perinatally infected youth (PIY) and those aged 15–24 as behaviourally infected youth (BIY), with the latter group divided into two subgroups, ages 15–19 BIY 1 and ages 20–24 BIY 2. Data was collected from the NHSO for patients initiated on ART between the ages of 10 and 24 years between 2008 and 2013. ART was defined by at least three drugs, including NNRTIs or PIs, and two or three NRTIs. Baseline figures were taken to be those on the date of ART initiation. Treatment failure at the first year of ART was taken to be a composite endpoint of either a VL ≥1000 copies/mL for those with VL testing or loss to follow-up (not having at least two CD4 cell count tests during follow-up) or death during the first year of treatment, or a major regimen switch between NNRTIs and PIs for those without VL tests.

A Cox regression model was used to assess predictors of mortality and loss to follow-up, and a logistic regression model used to assess predictors of treatment failure at the first year of ART initiation.

Most individuals in the study population were initiated on NNRTI-based ART regimens (93% in PIY, 78% in BIY 2 and 59% in BIY 1) with the lowest baseline median CD4 cell counts in the PIY group at 154 cells/mm^3 and highest in the BIY 1 group at 241 cells/mm^3 at ART initiation. The PIY group had the longest median duration of ART of 4 years (IQR 2–6 years) with this figure being 2 years in both the BIY 1 and BIY 2 groups.

Mortality rates (per 100 patient years) ranged from the lowest at 2.5 (2.2–2.9) in the PIY group to the highest at 3.1 (2.7–3.6) seen in the BIY1 group. Loss to follow-up (per 100 patient years) was highest in the BIY1 group at 13.9 (CI 12.9–14.8) compared to the lowest rates of 2.9 (CI 2.4–3.3) in the PIY group. No differences were seen between the PIY and BIY groups; however,

NNRTI-based first-line regimens, baseline CD4 cell counts <200 cells/mm^3 and loss to follow-up were factors found to be associated with increased risk of mortality on multivariate analyses. Factors found to be associated with loss to follow-up included being female, being on PI-based ART rather than NNRTI-based regimens, and progressively higher baseline CD4 cell counts directly correlating with likelihood of loss to follow-up. PIY were found to be more likely to have virological failure at 22% compared to 18% and 12% in the BIY 1 and BIY 2 groups, respectively. Similarly, higher likelihoods of treatment failure were associated with being female, in the BIY 1 or BIY 2 groups, and having a low baseline CD4 cell count (<200 cells/mm^3).

Compared to studies in Africa, this study found mortality rates were lower overall and loss to follow-up rates either similar or lower.

Marija Pantelic (Oxford University, UK) presented on the what constitutes adolescent-friendly health services [4]. Internalised HIV stigma is the acceptance of negative attitudes associated with HIV, such as feelings of shame and worthlessness. It is an important but understudied aspect of living with HIV that has large impacts on quality of life. Internalised stigma is a barrier to seeking treatment and prevention. Studies performed in South Africa, Burkina Faso and Kenya have all found that rates of internalised HIV stigma are higher than enacted stigma. There are emerging promising interventions for adults that have been tested in Africa utilising cognitive behavioural therapy, food utilisation and improving access to ART. However, little is known about the application of these techniques to the adolescent population.

No established programmes exist to reduce internalised HIV stigma in adolescents in sub-Saharan Africa and no qualitative studies have taken place in this age group. Ways in which current healthcare systems shape HIV stigma among adolescents living with HIV (ALHIV) include: having to miss school for treatments; leading to a sense of being different to others, being scolded at clinics; leading to a sense of self blame for their illness, and treatments being unavailable; which can lead to feeling that their health being unimportant.

This study looked at whether quality healthcare could protect against HIV stigma, ensuring ALHIV were not made to miss school for clinic appointments, and that they had supportive healthcare providers and well-stocked clinics. It was performed in an Eastern Cape health district in South Africa and recruited from 53 health facilities, (1060 ALHIV with 500 stigma controls). Community tracing was performed using standardised questionnaires. The study found that the individuals studied were more than three times more likely to report internalised stigma than discrimination. Approximately one-third had also perceived negative attitudes from the community and 7.4% experienced outright discrimination. In terms of quality of healthcare, 94.4% had reliable access to ART stocks, 64.8% to flexible appointment times and 80.9% had kind healthcare providers. However, only half of all those studied had all three of these available to them. Flexible clinic appointment times and having a reliable supply of ART were associated with a significant reduction in internalised stigma. Having kind and understanding healthcare providers nearly halved the odds of internalised stigma. Having a combination of all three of these factors reduced internalised stigma to one-third.

Adolescents need access to reliable, easily accessible ART, and need supportive healthcare providers who provide positive interactions. More research is needed on flexible and community-based clinic models of healthcare service delivery for ALHIV to minimise impacts of appointments on school attendance. There is currently a movement towards youth-led, high-quality, adolescent-sensitive healthcare provision and youth advocacy to address the needs of ALHIV.

Few data are available on young people's own experiences of transition or readiness to transfer to adult care. It is well known that self-efficacy in healthcare navigation is essential to maximise retention and adherence to HIV care. Factors such as speaking English as a second language, lower socio-economic status and poor literacy are known barriers to successful transitioning. The UK previously did not have a model for the transition of adolescents to transition to adult care with the current system transitioning patients based on individualised approaches.

Ali Judd (University College London, UK) presented a study of 13–21-year-old adolescents with perinatally acquired HIV across 13 clinics in England between 2013 and 2015, with follow-up interviews in 2016–2017, where researchers asked participants about their transition experiences [5]. The majority of those interviewed were in adolescent-specific clinics within adult care.

For those still in paediatric care, 89% had already discussed transitioning to adult care with their paediatric providers, mostly at a median age of 15 years. Three-quarters of adolescents already in adult care had been directly transferred to adult services at a median age of 17, whereas the remaining transitioned via shared-care clinics (with both paediatric and adult physicians in clinic) at a median age of 16 years. Most adolescents said they were very or quite prepared at the time of transfer. Half had a choice of where their care was transferred to. Only a small proportion of adolescents found adult care to be worse than paediatric care when comparing quality markers including times of clinic, support from staff, environment of clinic and how well the services met their needs. Of note, times of clinics and flexibility of appointment times were felt to be better in adult compared to paediatric services. Overall self-management of care by adolescents in adult clinics was found to be better, for example making their own appointments, travel plans and telling the clinic whether they needed more ART. Older ages were associated with higher self-management composite scores overall. The majority of adolescents in both paediatric and adult care reported high levels of satisfaction with their healthcare provision.

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Debate: should self-testing be implemented for all adolescents?

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In favour of self-testing, Cheryl Johnson argued that 30% of HIV infections are undiagnosed and many of these are adolescents [1]. There has been some programmatic success with door-to-door community-based testing; however, the new case detection yield is low and the 90% diagnosis target is a long way off. Importantly,

despite the lack of success in increasing diagnosis rate, 71% of countries currently require parental consent for adolescents under 18 years to receive an HIV test [1]. In a recent study, less than 60% of adolescents reported ever having tested and 50% of newly diagnosed cases in adolescents were first-time testers [2]. Finding the missing adolescents clearly requires a different strategy.

Studies have shown that adolescents rate the acceptability and desirability of self-testing as high and report that self-testing does overcome some of the barriers to conventional testing, particularly in countries where parental consent is required for testing [3]. Self-testing appears to be used by those very individuals who tend to avoid conventional healthcare settings, particularly self-conscious adolescents. In a recent study, highest uptake of self-testing was among 16–19-year-olds and 40% were first-time testers [4]. Two further RCTs showed high efficacy, measured as substantial (up to three-fold) increase in the number starting ART [3,5]. Cost-effectiveness is similarly high: while the initial unit cost of healthcare services will increase, the short- and long-term health benefits are substantial. In addition, the per-test cost has recently been reduced to under $2 [6,7]. No potential harm has been shown to have emerged from self-testing. In a recent study, there were no documented social adverse events for over 450,000 self-tests performed [3]. In contrast, undiagnosed HIV in adolescents has a high morbidity and mortality [1]. The majority of adolescents are able to perform the test correctly [8]. In fact, adolescents generally followed instructions better than adults [9]. Self-testing does not replace conventional testing but is rather complementary and still requires confirmation by a healthcare worker. In cases where there is some uncertainty about the self-test result, adolescents may be more likely to seek healthcare worker assistance than if they had not self-tested. Self-testing may help to empower adolescents, normalise HIV stigma and encourage adolescents to take responsibility for their own health. Finally, WHO have recommended self-testing in guidelines in general and, while adolescents are not specifically mentioned, it is generally accepted that they should be included [8].

Gabriel Chamie did not dispute the need for widespread accessible testing for adolescents; however, the risks of self-testing require further exploration, for the following reasons: It is not a given that an unsupervised positive test will lead to linkage to care [10,11]. In fact, self-testing may lead to reduced health care facility attendance resulting in lost opportunities for education and healthcare worker interventions [4]. Self-testing may lead to an increase in condomless sex after 'sero-sorting' [12] where the window period is not considered among potential couples [13]. In addition, it is possible that user error in technique may lead to false positive results [14]. In contrast, the benefits of testing by a healthcare worker include well-informed counselling and ongoing support to ensure linkage to care [15], as well as measurable outcomes regarding the success of the testing strategy [16].

In the end, there was general agreement that HIV self-testing should be made more widely available, particularly among adolescents.

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