UNICEF Learning Collaborative

Summary of Selected Research Articles

January to March 2019

Topic I: HIV Testing Strategies

Musarandega, Reuben, et al., 'Scaling up pediatric HIV testing by incorporating provider-initiated HIV testing into all child health services in Hurungwe District, Zimbabwe', *Journal of Acquired Immune Deficiency Syndromes*, vol. 77 (1), 1 January 2019.

- Results from an enhanced pilot programme on paediatric HIV testing in Zimbabwe demonstrated the feasibility and positive impact of integrating HIV testing into broader child health services. The programme was implemented by the Elizabeth Glaser Pediatric AIDS Foundation.
- Implemented in 33 health facilities, the pilot programme encouraged providers to expand HIV testing services for all children under 5 years old with unknown HIV status using any child health services; it also integrated HIV testing into immunization campaigns. Support visits and training were provided to staff at all participating facilities.
- More than 7,000 children aged 0–5 years were tested out of the 12,500 who attended a child health service facility. The number of children who tested positive during the 6-month programme increased by 55 per cent over the previous 6-month period in the same facilities. Among the 122 children who tested positive, 63 per cent would have been missed under existing testing guidelines.
- The authors point to the results as confirming that the impact of integrating HIV testing into all paediatric health services to identify children living with HIV is potentially greater than when HIV testing is integrated only with maternal health centres.

Mulubwa, Chama, et al., 'Community based distribution of oral HIV self-testing kits in Zambia: A cluster-randomised trial nested in four HPTN 071 (PopART) intervention communities', *The Lancet HIV*, vol. 6 (2), 1 February 2019.

- The HPTN 071 (PopART) study provided door-to-door HIV testing in 21 intervention communities in South Africa and Zambia. Nested within the PopART study, this cluster-randomized trial assessed the effect of offering self-testing kits on household members' knowledge of HIV status in four communities in Zambia.
- Communities in the trial were randomized to receive the standard PopART intervention with door-to-door home-based HIV testing administered by a health worker or a choice between the standard intervention and HIV self-testing kits. Participants who received the intervention with HIV self-testing could choose supervised or unsupervised use of the self-testing kit and could choose to receive an additional kit for secondary distribution to partners not present during the visit.
- Results showed that 9,027 of 13,267 household members who received HIV self-testing kits knew their HIV status compared with 8,952 of 13,706 members in the non-self-testing group (68 per cent vs. 65 per cent).
- Notably, the increase in knowledge of HIV status seen in this self-testing intervention was driven by more men knowing their status. In particular, men aged 30 years or older were

more likely to self-test unsupervised or with secondary distribution of HIV self-testing kits compared to younger men and women. The authors suggest that door-to-door distribution of HIV self-testing kits can help reach men who may be missed by other HIV testing services.

De Cock, Kevin, et al., 'Where are the positives? HIV testing in sub-Saharan Africa in the era of test and treat', *AIDS*, vol. 33 (2), 1 February 2019.

- In this commentary, the authors from the U.S. Centers for Disease Control and Prevention, the World Health Organization and ICAP at Columbia University discuss progress in and challenges of expanding HIV testing in the context of achieving the 90-90-90 treatment targets.
- Due to resource constraints, programmes increasingly are having to focus on building efficiencies and particularly on maximizing 'yield', the proportion of tests performed that are positive. The authors argue that there is a tension between HIV testing strategies aiming for high yield and those seeking to identify the largest absolute number of individuals living with HIV. Choosing one strategy over the other requires a focus either on rates or numbers, in consideration of costs. As countries move closer to global targets in prevention, they can expect a lower yield but they should not necessarily reduce the number of tests. Beyond yield, evaluation indicators like number of new HIV diagnoses, cost per HIV-positive individual identified and proportion linked to ART and rates of viral suppression are critical.
- The authors also remind programme planners and policy makers to be cautious about focusing only on highly targeted innovations and approaches, such as selective testing through the use of clinical algorithms, that prioritize specificity over sensitivity because these can miss asymptomatic or atypical individuals. While innovative approaches such as family and partner testing are important, their expansions should be at the expense of proven strategies such as provider-initiated testing and counselling in health facilities.

Frank, Simone, et al., 'Clinical effect and cost-effectiveness of incorporation of point-of-care assays into early infant HIV diagnosis programmes in Zimbabwe: A modelling study', *The Lancet HIV*, vol. 6 (3), 1 March 2019.

- The researchers conducted a modelling study to examine clinical benefits, costs and cost-effectiveness of replacing conventional early infant testing for HIV with point-of-care (POC) testing. They used data from a large-scale implementation of a POC early infant diagnosis (EID) programme in Zimbabwe.
- The model specifically looked at infants aged 6 weeks; its outcomes included survival, life expectancy and mean lifetime treatment cost. When conventional testing assays were used, projected life expectancy was 22.7 years for infants born with HIV and 62.5 years for all HIV-exposed infants; treatment cost was US$610 per HIV-exposed infant. When POC testing assays were used, projected life expectancy was 25.5 years among infants born with HIV and 62.6 years among all HIV-exposed infants; treatment cost rose to US$690 per HIV-exposed infant. Among infants born with HIV, survival at age 12 weeks was 76 per cent with conventional testing and 84 per cent with POC testing. This model demonstrated an incremental cost-effectiveness ratio of US$680 per year of life saved with POC early infant diagnosis.

- While treatment costs were higher, the results showed improvements in survival, life expectancy and cost-effectiveness with POC testing for infants at age 6 weeks compared to conventional testing in Zimbabwe. The study adds to the evidence base on the effectiveness of incorporating POC testing into early infant diagnosis programmes.

Topic II: Prevention of mother-to-child transmission of HIV (PMTCT)

Abrams, Elaine, et al., 'Impact of universal antiretroviral therapy for pregnant and postpartum women on antiretroviral therapy uptake and retention', *AIDS*, vol. 33 (1), 2 January 2019.

- The researchers used a stepped-wedge evaluation model to assess the extent to which maternal ART uptake and retention have improved in Eswatini as a result of the policy change to universal eligibility for lifelong ART (Option B+) from the previous standard of care, CD4-dependent ART eligibility (Option A). data from over 2,000 pregnant and breastfeeding women living with HIV.
- The assessment showed that under Option B+ guidelines, 94 per cent or nearly all women initiated ART compared to 36 per cent women under Option A. However, only 40 per cent of women in the study were retained in care through 6 months post-partum, consisting of 53 per cent of the Option B+ group and 23 per cent of the Option A group.
- The researchers remarked that compared with Option A, which included delays due to elibility screening and preparation time, Option B+ offered same-day initiation of ART, which might have been the driver of maternal ART uptake improvements. They note, however, that retention rates were unacceptably low across both options in this group of pregnant and breastfeeding women.

Choko, Augustine, et al., 'HIV self-testing alone or with additional interventions, including financial incentives, and linkage to care or prevention among male partners of antenatal clinic attendees in Malawi: An adaptive multi-arm, multi-stage cluster randomised trial', *PLoS Medicine*, 2 January 2019.

- This cluster randomized trial in Malawi assessed the impact of HIV self-testing alone or with other interventions on the uptake of testing and linkage to care among male partners of women attending antenatal care (ANC) clinics.
- Women attending ANC clinics with a primary male partner not known to be on antiretroviral therapy (ART) were enrolled. In the standard of care arm, women received a clinic invitation letter to share with their male partners; in the five intervention arms, women received HIV self-testing kits along with an additional kit for their partner, a financial incentive of $US3, a financial incentive of $US10, a lottery with a chance to win US$30 or a phone call reminder.
- Of more than 2,000 women enrolled in the trial, 44 per cent of their male partners had never received an HIV test. In all five intervention arms, higher proportions of male partners reported having completed HIV testing (87.0 to 95.4 per cent), compared with male partners in the standard of care arm (17.4 per cent). The highest proportion of male partners reporting having completed HIV testing was in the financial incentive intervention arm. Overall, 46 male partners tested positive and 91 per cent of them initiated ART within 28 days; 222 male partners tested negative and were not already circumcised. More than 60 per cent of these underwent voluntary male medical circumcision as part of the trial.

- The researchers noted that partner-delivered HIV self-testing was shown to be effective in increasing the likelihood of men's being linked to HIV care or prevention, especially when combined with financial incentives or phone call reminders.

Blanche, Stephane, et al., 'Growth in HIV-1-exposed but uninfected infants treated with lopinavir–ritonavir versus lamivudine: A secondary analysis of the ANRS 12174 trial', *The Lancet HIV*, Epub Ahead of Print, 24 February 2019.

- This secondary analysis compared the effects of lopinavir-ritonavir and lamivudine on growth (by weight and length) in HIV-exposed uninfected infants whose mothers were ineligible for ART in Burkina Faso, South Africa, Uganda and Zambia.
- The primary trial randomized participants into two groups receiving one of two regimens of infant prophylaxis at 7 days after birth to prevent HIV transmission through breastfeeding. One group of infants received lopinavir-ritonavir and the other group received lamivudine. The secondary analysis collected these infants' lengths and weights from the time of treatment initiation until the cessation of breastfeeding at 12 months.
- Of more than 1,200 infants in the study, the weight-for-age and weight-for-length scores were significantly lower in the lopinavir-ritonavir group than in the lamivudine group. This pattern was consistent at age 26 weeks and at age 50 weeks. The lopinavir-ritonavir regimen was associated with decreases in weight-for-age and weight-for-length over time. Notably, the differences between the two treatment groups occurred primarily at early stages immediately after initiation of treatment.
- The authors claim that the trial design allowed them to assess an association between the two treatments and the differences seen in growth. The lower weight gain in infants who received lopinavir-ritonavir compared with those who received lamivudine is relevant to consider for recommendations about early treatment of HIV-exposed infants.

Zhang, Lei, et al., 'Integrated approach for triple elimination of mother-to-child transmission of HIV, hepatitis B and syphilis is highly effective and cost-effective: An economic evaluation', *International Journal of Epidemiology,* Epub ahead of print, 16 March 2019.

- Globally, frameworks for the triple elimination of mother-to-child transmission (EMTCT) of HIV, hepatitis B and syphilis have been proposed and endorsed by many health agencies. This study assessed population-level impacts and cost-effectiveness of the integrated approaches encouraged by these triple elimination frameworks using simulated data from Cambodia.
- Currently, the PMTCT programme costs an estimated US$2.3 million per year for about 370,000 pregnant women in Cambodia. Through this programme, 87 per cent of women attending ANC services are screened for HIV and 43 per cent are tested for syphilis.
- Integrating HIV and syphilis in the ANC setting was shown to reduce time-costs for health care workers by 19 per cent. It also improved the MTCT rate for HIV from 6.6 per cent to 6.1 per cent and the MTCT rate of syphilis from 9.4 per cent to 4.6 per cent. The integration resulted in cost savings of US$380,000 per year.
- The researchers found that adding hepatitis B screening and care increased personnel costs but the integrated approach remained cost-effective when considering disability-adjusted life years saved.

- The study provides additional evidence for policymakers that integrating EMTCT programmes for HIV, hepatitis B and syphilis into ANC settings is a cost-effective strategy. Multiple scenarios for integration, such as those based on varying eligibility for ART among women and infants, may be effective in meeting elimination targets and reaching cost savings depending on the local setting.

Topic III: Paediatric and Adolescent Treatment of HIV

Gandhi, Monica, et al., 'Validation of a Urine Tenofovir Immunoassay for Adherence Monitoring to PrEP and ART and Establishing the Cut-Off for a Point-of-Care Test', *Journal of Acquired Immune Deficiency Syndromes,* Epub Ahead of Print, 1 January 2019.

- Currently, adherence to pre-exposure prophylaxis (PrEP) and ART is generally self-reported in both research and treatment settings. This study tested a low-cost, point-of-care (POC) monitoring tool for real-time assessment of the use of PrEP and tenofovir-based ART in Thailand.
- The researchers collected urine samples from participants enrolled in the TARGET study, a randomized open-label study of tenofovir in healthy adult volunteers uninfected with HIV in Thailand. The new POC immunoassay measured antibodies to tenofovir and a regression model was used to determine a minimum cut-off value for an individual's dosage.
- A cut-off of 1,500 nanograms per milliliter accurately identified 98 per cent of patients who took a dose within the previous 24 hours. Notably, the test had high sensitivity (94 per cent) and specificity (99 per cent); its accuracy correlated well to current antibody assays that served as the "gold standard" in this trial.
- These results signal a promising innovation to track adherence that is low-cost and provides fast results, enabling providers to offer adherence support to individuals in ways that are more efficient and less labour-intensive.

Vieira, Vinicius, et al., 'Strong sex bias in elite control of paediatric HIV infection', *AIDS*, vol. 33 (1), 2 January 2019.

- This report aimed to describe the characteristics of "paediatric elite controllers", children who have a vertically transmitted HIV infection, are not on ART and had consecutive viral load measurements below the limit of detection for over a year. The study examined 10 cohorts of HIV-infected children from Brazil, South Africa, Spain, Sweden, Thailand and the United Kingdom.
- Eleven paediatric elite controllers, who had never received ART, were identified from the cohorts; 8 children born in Africa, 2 in Latin America and 1 in Asia. Of note, 10 children were female and only 1 was male. Control of viraemia was achieved at a median age of 6.5 years. Based on this data, which included 22,681 children who did not match the criteria for being an elite controller, the authors estimated the prevalence of paediatric elite controllers to be 5- to 10-fold lower than in adults, among whom elite controllers constitute approximately 0.5 per cent of infections.
- Compared to the documentation of adult elite controllers, there are very little data on immune control of HIV in paediatric infection. The increased prevalence of elite controllers among females, as seen here, is a start to identifying the potentially unique characteristics

of paediatric elite controllers. A better understanding about paediatric elite control can be critical for research about paediatric HIV treatment and cure.

Phillips, Andrew, et al., 'Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: A modelling study', *The Lancet HIV*, vol. 6 (2), February 2019.

- The authors used an existing model of HIV transmission, progression and impact of ART in individuals to compare drug regimens using dolutegravir in sub-Saharan Africa. The modelling study aimed to inform policymakers and other stakeholders on the use of dolutegravir for the greatest public health benefits while balancing risks, such as a possible increased risk of neural tube defects suggested by a previous study. Around 1,000 potential settings were generated, with such varying parameters as rates of HIV testing, adherence, ART interruption and switching of regimens.
- The modelling study found that a policy of tenofovir, lamivudine and dolutegravir for all individuals on ART gives the best overall improvement in health outcomes, viral suppression and MTCT rate when compared with three alternatives: (1) efavirenz-based first-line ART, (2) a regimen of tenofovir, lamivudine and dolutegravir that is dependent on confirmed viral suppression, and (3) the same regimen only for women who do not want more children.
- The combined benefits of wider dolutegravir use was shown to offset the risk of neural tube defects. Transitioning to this regimen for all people on ART was also seen to be cost-saving over 20 years. These modelling results support dolutegravir use in sub-Saharan Africa and provide quantitative evidence to guide policies.

The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration, 'Incidence of switching to second-line antiretroviral therapy and associated factors in children with HIV: An international cohort collaboration', *The Lancet HIV*, vol. 6 (2), 1 February 2019.

- This global paediatric analysis from 12 observational cohort networks in the CIPHER collaboration quantified cumulative HIV incidence when children were switched to second-line ART in order to inform the need for paediatric second-line formulations. Notably, around 90 per cent of the more than 93,351 children from the CIPHER collaboration were from sub-Saharan Africa.
- In the study cohort, 89 per cent of children were initiated on a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and 11 per cent on a protease inhibitor regimen. Overall, 4 per cent (3,883) of children were switched to second-line ART after a median of 35 months.
- The study determined both cohort-level factors and individual-level factors associated with the likelihood of switching to second-line ART. The former included being in a higher-income country and having programmes for routine or targeted monitoring of CD4 and viral load compared to CD4-only monitoring. For individuals, being male and older at ART initiation as well as beginning with an NNRTI-based regimen were significantly associated with the increased likelihood of switching.
- Notably, the study found significant variations in how often children are switched to second-line ART across geographical regions due to varying monitoring strategies. Three years after ART initiation, switching was least common among children in geographical regions with clinical-only monitoring, such as parts of sub-Saharan Africa. This suggests that scaling up

viral load monitoring, particularly in low-income countries, will increase demand for second-line ART formulations for children.

Van de Wijer, Lisa, et al., 'Neuropsychiatric symptoms in Tanzanian HIV-infected children receiving long-term efavirenz treatment: A multicentre, cross-sectional, observational study', *The Lancet HIV*, Epub Ahead of Print, 12 February 2019.

- This cross-sectional observational study enrolled HIV-infected children aged 6–12 years who were registered at HIV clinics in the United Republic of Tanzania and received efavirenz or another antiretroviral medicines (ARVs). It described the effects of efavirenz on a range of outcome measures including behaviour, memory, cognitive ability and school performance. This study is the first comprehensive psychiatric evaluation of children on efavirenz in sub-Saharan Africa.
- Children on efavirenz showed more internalizing behaviours, defined in the study as including anxiety and difficulty concentrating at school, and poorer school performance compared to peers on other ARVs espite all children in the study showing similar cognitive abilities. Notably, the children studied were also different in other characteristics; there was a higher prevalence of parental loss and less HIV status disclosure among children receiving efavirenz compared to those on alternative ARVs.
- The researchers highlight the need for more behavioural studies in children comparing efavirenz to other ARVs. They maintain the importance of efavirenz as a key paediatric treatment option, but point to a need to continue to assess and follow up on neuropsychiatric symptoms, especially as newer drugs enter the market.

Martinez de Tejada, Begoña, 'Birth defects after exposure to efavirenz-based antiretroviral therapy at conception/first trimester of pregnancy: A multicohort analysis', *Journal of Acquired Immune Deficiency Syndromes*, vol. 80 (3), 1 March 2019.

- The researchers conducted a pooled analysis of seven observational studies from 13 European countries and Thailand to examine associations between efavirenz use during conception or first trimester of pregnancy and the occurrence of birth defects. The study sought to add to the discussions around the safety of newer ART regimens for pregnant women, following questions raised on dolutegravir usage by the Tsepamo study in Botswana.
- Of about 21,000 women in the studies, 30 per cent were on a non-efavirenz ART regimen and 5 per cent were on efaviranez; 65 per cent were unexposed to ART at conception and first trimester. The overall prevalence of birth defects in the study cohort was 1.65 per cent. To note, the prevalence of birth defects after exposure to efavirenz was not statistically different from the prevalence after exposure to non-efavirenz regimens.
- The researchers concluded that these data suggest efavirenz is at least as safe as other ART drugs currently recommended for antenatal use. However, most of the studies did not report stillbirths and terminated pregnancies, which could have led to underreporting birth defect risks in this analysis.

Flynn, Patricia, and Elaine Abrams, 'Growing up with perinatal HIV', *AIDS*, vol. 33 (4), 15 March 2019.

- This commentary, drawing on data from the CIPHER global cohort collaboration, examines disparities in morbidity and mortality of children with perinatal HIV infections across geographies, despite global improvements in ART and trends in initiating treatment at younger ages.
- The CIPHER data included more than 38,000 adolescents with perinatal HIV. Of these, 79 per cent were from sub-Saharan Africa. Overall, 88 per cent of the adolescents received ART, but only 38 per cent had at least one viral load measurement and only 70 per cent of those demonstrated viral suppression. Older adolescents in particular had low rates of viral load suppression and were more likely to have started ART later in life.
- The authors note that both HIV infection and HIV treatment can affect critical periods of growth and development in children and adolescents. Studies have shown decreases in bone mineral density, metabolic adverse effects and negative impacts on the developing brain. The most commonly cited deficiencies in adolescents with perinatal HIV relate to executive functions, including memory, attention, speed of processing information and other complex cognitive functions. These have also been linked with poor adherence to medications and increased risk-taking behaviours.
- As more children with perinatal HIV infection age into adolescence and young adulthood, they will need additional attention and innovations in HIV care and treatment. Despite improved therapies and longer life spans, new complications and co-morbidities might emerge during the aging process.

Topic IV: HIV prevention in adolescent girls and young women

Stoner, Marie, et al., 'Age-disparate partnerships and incident HIV infection in adolescent girls and young women in rural South Africa', AIDS, vol. 33 (1), 1 January 2019.

- Using longitudinal data from a separate randomized trial examining the use of cash transfers to reduce HIV risks among adolescent girls and young women (AGYW), the researchers assessed the association between age-disparate relationships and incident HIV infections among AGYW in South Africa.
- Age-disparate relationships were defined as relationships in which the male partner was 5 or more years older than the adolescent. The risk of incident HIV infection increased over time and was higher among AGYW in age-disparate relationships compared to AGYW in relationships with partners of similar age. Notably, differences between the two groups became more pronounced as time went on in the study. By the end of the study period, at 5.5 years since enrolment, AGYW with an age-disparate partnership had a 12.6 per cent higher risk of HIV than AGYW without age-disparate partnerships.
- The differences remained significant after adjusting for transactional sex and condomless sex. The researchers suggested that increased risk of HIV incident infection is driven by greater exposure to men in a higher HIV prevalence pool rather than risk behaviours within age-disparate relationships.

Meinck, Franziska, et al., 'Does free schooling affect pathways from adverse childhood experiences via mental health distress to HIV risk among adolescent girls in South Africa: A longitudinal moderated pathway model', *Journal of International AIDS Society,* vol. 22 (3), 14 March 2019.

- This study aimed to develop an empirical model describing a link between adverse childhood experiences, mental health distress and HIV risk behaviour among adolescent girls in South Africa with the goal of examining the mediating effects of free schooling provisions.
- More than 3,500 adolescents aged 10–17 were recruited from urban and rural areas in South Africa and interviewed at baseline and follow-up after one year. Adverse childhood experiences included the following measures: lifetime child abuse, exposure to poverty, AIDS in the family and witnessing domestic violence. Internalized mental health distress included measures for depression, anxiety and suicidality, while externalized mental health distress included measures for alcohol and drug use, behaviour problems and peer relationship problems. HIV risk behaviours included infrequent condom use, sex with drug or alcohol use and multiple partners.
- The empirical model developed in this study showed multiple pathways of vulnerability that led to increased HIV risk behaviours, but notably, it showed no significant direct pathways between adverse childhood experiences and HIV risk behaviours.
- The researchers noted that the relationship between adverse childhood experiences and HIV risk behaviours was fully mediated by mental health distress. This provides an opportunity to intervene in the pathway towards HIV risk behaviors by lowering mental health distress. This study provided evidence that free schooling is associated with lower externalizing of mental health distress among adolescents and can thus have an impact on HIV risk behaviours.

The research in this issue was summarized by Carthi Mannikarottu, Mar. 2019.