



The Southern African HIV Clinicians' Society and the Southern African Journal of HIV Medicine

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South Africa
May 2020

Dear Colleagues and Readers of the Southern African Journal of HIV Medicine

- 1. The Editor's Review of articles published from August-December 2019 in the S Afr J of HIV Medicine.**
- 2. An Urgent Call for Articles/Original Research/Reviews in the Field of COVID19 and HIV Medicine**

1. Please take a look at the following **summaries** of articles that appeared in the second half of the 2019 edition of the SAJHIVMED. Hopefully, you will want to take a look at the original article. The link to the article is provided after each heading. These articles reflect the evolving nature of the southern African HIV epidemic. Most represent original research. We published two guidelines in 2019 viz. The 2019 Updated Management of Cryptococcal Infection and The Palliative Care of the HIV Infected. I have not summarized them further as they are summaries of current science. However, I suggest reading the guidelines for yourself. Will South Africa reach the UNAID's 90-90-90% goals by 2030? Read the articles and think about the road ahead. We have a decade left. But recall that these goals were originally meant to have been realized in 2020. There is still a lot to be done if we are to end the HIV epidemic. The SAJHIVMED will keep you updated with local data. Enjoy browsing through the journal and these 2019 August-December summaries.
2. A Call for Articles dealing with COVID19 and HIV. The Southern African Journal of HIV Medicine and the Southern African HIV Clinicians' Society, wish to inform you of our rapid-access project to fast-track the publication of articles/research material/studies/basic science papers that deal with the African HIV and COVID19 epidemics. The SA Clinicians' Society and Journal are collaborating with AOSIS, our publishers, to facilitate the rapid publication of COVID19/HIV material. We are aware that fellow scientists will wish to get their manuscripts into an internationally accredited journal as quickly as possible. The SAJHIVMED has international accreditation. Manuscripts will be reviewed by senior academics nationally and internationally and channelled into a fast-track edit-unit. The process will be directed by myself and my colleagues in AOSIS.

Dave Spencer

Editor-in-Chief, SAJHIVMED May 2020

The Editor's Review of articles published from August-December 2019 in the S Afr J of HIV Medicine.

August 2019

1. Woods J, Moorhouse M, Knight L. A descriptive analysis of the role of a WhatsApp clinical discussion group as a forum for continuing medical education in the Eastern Cape, South Africa. SAJHIVMED /Vol 20, No 1 / a982 / 01 August 2019.
<https://doi.org/10.4102/sajhivmed.v20i1.982>.

Editor's comment: In the year following my internship (1976), I worked at Mseleni Hospital, then a small 120-bed hospital in a remote corner of KwaZulu Natal (KZN), SA. For much of the time, I was the only doctor. One of the highlights was the Thursday night radio call-in to discuss cases with colleagues at Manguzi and Bethesda, similar rural hospitals in northern KZN. I was a rookie. Darryl Hackland and Pat Garde (Bethesda) and Cliff Allward (Manguzi) were my life-line. Another was the periodic weekend fly-in of Durban-based University of KZN academics who would assist with surgery and walk through the wards with me.

This observational study of the role of a WhatsApp group gives that story a 21st-century twist. The goal of the authors was to assess the **educational value** of a WhatsApp group of n=166 experienced and inexperienced doctors in rural public hospitals and clinics in the Eastern Cape and to ask whether the WhatsApp discussion was helpful and whether **informed consent and privacy rules** were breached. All the patients had complicated HIV/TB co-infection. The study was undertaken between January 2016 and July 2017. The WhatsApp group were given a short questionnaire and asked to submit answers anonymously. Although 86% of respondents replied that the group had given them 'improved confidence and ability in managing sick patients', and 52% said they used the guidance they had received "all the time", many in the WhatsApp group, n=74/166 (45%), never actually posted a response. And while answers such as "I use the guidance to manage patients", "I refer to previous WhatsApp cases", "I gained new clinical insights" etc., reached statistical significance i.e. suggested that clinical confidence had been increased, high odd's ratios and wide confidence intervals suggest important limitations. (Study Table 3) Does posting patient-data risk a breach of doctor-patient ethics? 89% of respondents agreed that informed consent would be required before posting patient-related material, yet in real-time only 52% did this. And what about those registered on the programme who never appeared to participate? Was this a valuable learning experience for them? Perhaps an analysis of the differences between the 50% who didn't post cases and the 3% who did so frequently i.e. 6-10 times, might answer this question.

2. Mugusi SF, Mopei N, Minzi O. Adherence to combination antiretroviral therapy among orphaned children in Dar es Salaam, Tanzania. SAJHIVMED / Vol 20, No 1 / a954 / 06 August 2019. <https://doi.org/10.4102/sajhivmed.v20i1.954>.

Editor's comment: Adherence to ART is examined in this cross-sectional study of n=216 Tanzanian orphans aged 2-14 years. All the children were HIV-infected and had been on nevirapine (NVP)-based ART for a minimum of 6 months. The study was conducted from June -September 2015.



Adherence was measured in three ways: a 3-day recall of pill-taking behaviour (caregiver questioned), the historical regularity/reliability of clinic attendance, and the monitoring of NVP-blood levels on study entry. Viral load levels are not supplied. Likely not available. On recall, 79.6% of the children had not missed any doses. 82.9% gave a history of regular clinic attendance. Yet therapeutic levels of NVP viz. $\geq 3\mu\text{g/mL}$, were detected in only 72.2%. On multivariate analysis, higher NVP levels were protective of unreliable clinic attendance (unadjusted uOR 0.45, 95% CI 0.21-0.95, $p=0.04$) and linked positively to higher CD4 levels viz. $>25\%$ and counts $>500\text{ cells/mm}^3$, $p=0.001$. Orphans missing both parents were at greater risk of low NVP blood levels viz. uOR 1.37, 95% CI, 0.69-2.68. Sub-therapeutic NVP levels were less likely among those orphans who were aware of their HIV status i.e. had experienced full disclosure. uOR 0.65, 95% CI, 0.34-1.24. The limitations of this study are important: the cross-sectional design, the absence of an age-matched 'non-orphan' comparator-arm, reliance on caregiver 'self-reporting', and the wider lack of applicability of blood NVP levels to adherence management in Africa. The fact that viral loads are still not routinely available everywhere in sub-Saharan Africa is an inescapable subtext to this study. Is therapeutic NVP-monitoring needed in Africa? It added value to this study. But a wider role will be limited by costs and accessibility.

3. Vujanovic M, Brkic-Jovanovic N, Ilic D, Drvendzija Z, Srdic-Galic B, Turkuklov V, Brkic S, Maric D. Associations of visceral fat thickness and anthropometric measurements with non-alcoholic fatty liver development in male patients mono-infected with human immunodeficiency virus. SAJHIVMED /Vol 20, No 1 / a968 / 07 August 2019.
<https://doi.org/10.4102/sajhivmed.v20i1.986>.

Editor's comment: In this article from Serbia, 88 HIV-infected men on ART were enrolled in a study evaluating a link between visceral fat thickness (VFT) as measured with abdominal ultrasound and the routine anthropometric measurements of obesity, cardiovascular risk and non-alcoholic steatohepatitis (NASH). The study took place over 18 months between September 2016 and April 2018. The average age of the men was $39.9 \pm 9.9\text{yr}$ and the following anthropometric measurements were taken: waist and hip circumference (WC, HC), waist-hip and waist-height ratios (W/HipR, W/HtR) and the body mass index (BMI). Hepatic steatosis was diagnosed on sonography. Those with steatosis were more likely to have elevated random blood glucose levels, raised BMI, and raised WC, HC, W/HipR and W/HtR in addition to elevated VFT, $p<0.001$. Age ≥ 38.5 years was associated with increased risk; 90.6% of those aged $>38.5\text{ yr}$ with a VFT $>31.98\text{mm}$ had hepatic steatosis. The authors discuss these results in the context of low and middle-income countries where access to reliable non-invasive tests for hepatic steatosis is limited. Study limitations include the cross-sectional design, the absence of women and children and the lack of detailed information on the ARVs used by the men and the duration of their treatment.

4. Diana NE, Feldman C. Measles in adults: A comparison of hospitalized HIV-infected and HIV-uninfected patients. SAJHIVMED / Vol 20, No1 / a877 / 13 August 2019.
<https://doi.org/10/4102/sajhivmed.v20i1.877>.

Editor's comment: South Africa experienced an unusually large outbreak of measles between 2009 and 2011. In this descriptive paper from the wards of the Charlotte Maxeke Johannesburg Academic



Hospital, the authors present data on HIV-infected adults with laboratory-confirmed measles. 33 adults with measles were identified, of whom 24 underwent HIV testing: n= 18/24 (75%) were positive, 6 were HIV-negative. The remainder of the adult measles group (n=9) were not tested. Most of the HIV-infected were female: n=13/18 (72%). Although the authors remark that demographics, clinical findings and laboratory data between the HIV+ve and HIV-ve patients were similar, serious disease e.g. pneumonia and respiratory failure, was more frequent in the HIV infected [OR 5.0, 95% CI 0.48-51.8, p=0.34]. The duration of hospital stay of the HIV infected was significantly longer, p=0.03, and of the 3 adult-measles deaths, *all* were in the HIV-infected, [OR 2.9, 95% CI, 0.13-65.3, p=0.56]. The median CD4 count of the infected was 109 cells/mm³. Unfortunately, the authors do not provide further analysis e.g. individual CD4s, viral loads, the ART used and the microbiology of the secondary infections. Do HIV-infected adults exposed to measles require re-vaccination or vaccination if this was missed in childhood? This is not addressed in this paper. Its an important question. "The measles vaccine should be given to potentially susceptible but asymptomatic HIV-infected adults and be considered for those with symptomatic HIV infection even if NOT severely immunosuppressed". (Loevinsohn, 2019)

Loevinsohn G, et al. Measles Seroprevalence and Vaccine Responses in Human Immunodeficiency Virus-infected Adolescents and Adults: A Systematic Review. *Clin Infect Dis* 2019 Aug 16; 69(5): 836-844. doi:10.1093/cid/ciy980. High-level overview.
Moss WJ. Measles. Seminar. Lancet 2017;390: 2490-502. [http://dx.doi.org/10.1016/S0140-6736\(17\)31463-0](http://dx.doi.org/10.1016/S0140-6736(17)31463-0). Very readable overview.

Measles vaccination: A WHO position paper. April 2017. Recommendations. *Vaccine* 2019 Jan 7;37(2): 219-222. Doi.10.1016/j.vaccine.2017.07.066). Excellent.

5. Van Elsland SL, Peters RPH, Grobbelaar C, Ketelo P, Kok MO, Cotton MF, van Furth AM. Disclosure of human immunodeficiency virus status to children in South Africa: A comprehensive analysis. *SAJHIVMED* / Vol 20, No 1 / a884 / 22 August 2019. <https://doi.org/10.4102/sajhivmed.v20i1.884>

Editor's comment: Recommended reading. In this cross-sectional study from the Western Cape, the authors ask the following questions: how many children know their HIV status and what factors assist our understanding of non-disclosure? It's a well-written report with data that deserve a wide audience. The total cohort, n= 185. All were on ART and their ages ranged from 3-14 years. Most, n=145 (76.3%), had not experienced full disclosure. Seventeen (8.9%) had. A further 28 (14.7%) received 'partial' disclosure. The cross-sectional nature of the study, the small number of 'disclosed' children and the dependence on questionnaires, clinic records and caregiver's reports would have introduced limitations but the take-home messages are worth noting: disclosure was more likely to have occurred among older children and those whose caregivers were more highly educated. The latter were more likely to be male though less than 10% of the study's caregivers were men. Indeed disclosure was less likely if the caregiver was female, if children had detectable viral loads and if the child was still taking 'syrup' formulations of the ARVs viz. a younger group, if the child was noted by the caregiver to be non-adherent and if the child was on protease inhibitors (PIs), stavudine (d4T) and/or didanosine (ddI). The writing is clear and this paper provides the reader with credible information. Figure 1 will also give HIV-educators a useful outline of the important associations of disclosure/non-disclosure.



6. Schutz C, Ward A, Burton R, Nicol MP, Blumenthal L, Meintjes G, Kerkhoff AD. False rifampicin results using Xpert MTB/RIF on urine samples in hospitalized HIV-infected patients. SAJHIVMED / Vol 20, No 1 / a978 / 28 August 2019.
<https://doi.org/10.4102/sajhivmed.v20i1.978>

Editor's comment: Recommended reading. This study is from colleagues in the Cape. Urine samples were collected prospectively from HIV-infected patients with microbiologically proven active TB in two independent cohorts between 2012 and 2016. Multiple samples from each patient - including sputum, blood, tissue and urine - were subjected to culture, gene Xpert (including Xpert Ultra) and line probe analysis (LPA). A total of 1704 urine Xpert results were available from n=1171 patients. **n=416, 24.4%** [95% CI 22.4-26.5] **of the urine Xpert results were positive for *Mycobacterium tuberculosis* (MTB). 43/413 (10.4%) were rifampicin-resistant on Xpert.** Of the latter group, 30/41 were confirmed to be truly rifampicin-resistant yielding a positive predictive value of 73.2% [95% CI, 57.1-85/8]. Urine tests from patients *NOT on TB therapy* at the time of assessment gave more true-positive rifampicin-resistant Xpert results (85.7%, 95% CI 67.3-96.0) than the urine of those on TB treatment (53.8%, 95 CI 25.1-80.8). **11/43 urine results were falsely positive for rifampicin-resistance: 25.6%, 95% CI 13.5-41.2.** Three patients in the **urine Xpert rifampicin-resistant** group were found to have **concurrent rifampicin-sensitive TB** on alternative specimens tested simultaneously i.e. "**hetero-resistant TB**". The authors provide a paper that gets to the point and feeds the reader's mind. A stimulating read. **Compulsory reading for clinicians particularly, HIV and ID colleagues, fellows and registrars!!**

7. Ekermans P, de Gama R, Kock C, Hoosien E, Slavik T, Marshall T, Corcoran C, van Ingen J. An unusual case of abdominal mycobacterial infection: case report and literature review. SAJHIVMED / Vol 20, No 1 / a993/ 28 August 2019.
<https://doi.org/10.4102/sajhivmed.v20i1.993>.

Editor's comment: Highly recommended. In this case report, Dr Ekermans and colleagues describe an HIV-infected 8-year-old's experience of AIDS in South Africa. The author does a great job of describing the difficulties in confirming the diagnosis and isolating the organism. The histological and radiographic plates are superb: clear and compelling. The author tells this story with compassion and respect for his subject. The art and science of medicine shine on these pages. This is how we learn medicine. And how we become better doctors. I loved this read and recommend it to all who read this journal.

8. Atuhaire C, Taseera K, Spoor C, Cumber RY, Cumber SN. Knowledge and perceptions of male immigrants in Leeds (UK) towards male circumcision as an HIV-prevention strategy. SAJHIVMED 2019/ Vol 20, No 1 / a823/ 28 August 2019.
<https://doi.org/10.4102/sajhivmed.v20i1.823>

Editor's comment: While the estimated prevalence of HIV infection in the UK is low viz. ≤ 1.5 per 1000 persons, that of UK immigrants from Eastern and Southern Africa is far higher viz.

25-50 per 1000 persons. Would medical male circumcision be considered by these immigrants as a means of preventing HIV transmission? Only 10 persons were interviewed in a snowball recruitment study of contacts from a local church in Leeds, UK. These expressed little or no knowledge of circumcision as an HIV-preventive tool. Instead and despite the group's roots from epidemic's epicenter, circumcision is still merely a 'rite-of-passage'. While the limitations of this study are obvious, it begs the question of the universality of HIV-dogma. In the West, "Treatment as Prevention" has replaced medical male circumcision (MMC). With current dogma promoting universal "test and treat (UTT)" and "immediate ART for all", should we be talking about MCC in high-income countries? And what of its future in middle and low-income regions in the face of more effective preventive measures? And how effectively has MMC changed attitudes to HIV prevention in East and Southern Africa?

September 2019

9. Manickchund N, du Plessis C, John M-A, Manzini TC, Gosnell BI, Lessell RJ, Moosa YS. Case report. Emtricitabine-induced pure red cell aplasia. SAJHIVMED 2019 /Vol 20, No 1 / a983 / 23 September 2019. <https://doi.4102/sajhivmed.v20i1.983>

Editor's comment: The authors report a patient with pure red-cell aplasia. The female was 35-years of age in 2014, pregnant, anaemic at baseline [Haemoglobin (Hb.) = 8.2 g/dL] and had a low CD4 count viz. CD4 = 83 c/mm³. Two months after starting first-line ART viz. tenofovir + emtricitabine (FTC) + efavirenz, she was found to be severely anemic: Hb.=2.2 g/dL, normocytic normochromic. Her HIV-infection was under control. Workup included a bone marrow examination that revealed a pure red cell aplasia and a positive parvovirus B-19 PCR. The patient received intravenous immune-globulin (IVIG) for 5 days and packed red cells. Over the next 11 months, she required multiple transfusions and 6 more courses of IVIG. Her ART was changed and the FTC stopped: tenofovir + abacavir + efavirenz. The anaemia resolved. The patient's parvovirus B19-PCR remained positive (2017). A role for lamivudine (3TC) and emtricitabine (FTC) in pure red cell aplasia has been suggested by multiple reports over the past two decades. This report is a reminder of this rare drug-related toxicity.

Suggested additional reading:

- Tsukamoto T. Hematopoietic Stem/Progenitor Cells and the Pathogenesis of HIV/AIDS. *Front Cell Infect Microbiol* 2020 Feb 21; 10:60. Doi:10.3389/fcimb.2020.00060.
- Durandt C, Potgieter JC, Mellet J et al. HIV and haematopoiesis. *S Afr Med J* 2019 Sep 10; 109 (8b): 40-45. Doi.10.7196/SAMJ.2019.vi09:8b.13829.
- Knuesel SJ, Sawalla Guseh II J, Karp Leaf R, Ciaranello AL, Eng GM. Case 6-2018: A 35-Year-Old Woman with Headache, Subjective Fever, and Anemia. *N Engl J Med* 2018; 378: 753-60. DOI:10.1056/NEJMcp1712223.



10. Cloete CM, Hampton J, Chetty T, Ngomane T, Spooner E, Zako LMG, Reddy T, Luthuli N, Ngobese H, Ramjee G, Coutsooudis A, Kiepiela P. Evaluation of a health system intervention to improve virological management in an antiretroviral programme at a municipal clinic in central Durban. SAJHIVMED /Vol 20. No 1/ a985/ 26 September 2019.

<https://doi.org/10.4102/sajhivmed.v20i1.985>

Editor's comment: "What are the gaps in service-delivery that allow for clinical failure/poor viral control?" This is a detailed, prospective clinic-based study undertaken between 2011-2015. The investigators divided the study into three periods: pre-intervention, intervention and post-intervention. The intervention required checking every 10th patient-file (n=1538) with (1) an in-depth file review, (2) recording of viral loads (vl) and the 'retention-in-care' status of the client and (3) an assessment of the "viral load-management process". Gaps were identified and interventions implemented. Outcome measurements improved over the 4 years of the study viz. the number of appropriate vl tests and the filing of results increased from 78% to 92% (p=0.0009), the number of patients who accessed their vl result increased from 59% to 86% (p<0.0001), and fewer, from 81% to 27%, required changes to ART following the intervention. The detail in this report suggests a huge commitment from the clinic staff and the research team. Sustainable? The study required outside funding and the salaries of additional staff. Sustainable? Gaps are noted: continuing high patient volumes, the ongoing and urgent priority of ART-initiation, the need for and absence of dedicated pharmacists in HIV clinics etc. The authors point out that the third UNAIDS 90 (95)% goal is achievable i.e. reliable long-term vl suppression by 2030. This sounds optimistic. "Is this effort reproducible on a large scale?"

11. Kummerow M, Shaddock EJ, Klipstein-Grobusch K, Barth RB, Grobbee DE, Venter DWF, Feldman C, Vos A. Unexpected low frequency of respiratory symptoms in an HIV-positive urban sub-Saharan population compared to an HIV-negative control group. S Afr J HIV Med 2019/Vol 20, No 1/a1010/ 26 September 2019.

<https://doi.org/10.4102/sajhivmed.v20i1.1010>

Editor's comment: This is a cross-sectional study of 547 adults living in Johannesburg between July 2016-November 2017. Two-thirds were PLWH (n=347, 63%). The remainder were HIV-uninfected matched controls. The median age was 37 years. Two-thirds (62%) were female. Recruits were asked about cough, cough accompanied by mucus/phlegm, breathlessness, wheeze etc. Participants were also examined, had blood tested (HIV-status confirmed, HIV-viral load, vl, CD4 cell count) and completed a 'quality of life' questionnaire. The PLWH were subdivided into groups: 'the ART-naïve' (26%), 'on first-line ART' (24%) and 'on second-line ART' (50%). Those on ART were recruits from randomised controlled trials (RCTs) and demonstrated a high level (>90%) of viral suppression. Their CD4 levels (median) were largely normal: viz. first-line ART, CD4 = 413.5 (range: 278.5-574.3) and second-line ART, CD4 = 619 (429-798) cells/mm³ respectively. Those 'initiating' therapy i.e. naïve to ART when tested also demonstrated relatively preserved median CD4 levels viz. CD4= 281 (range, 191-400.8) c/mm³. And indeed the authors note that "the frequency of respiratory symptoms did not differ by HIV status after adjustment for age and sex." "Breathlessness (however) was associated with older age, female sex, obesity, a previous history of respiratory infection and airway hyper-reactivity (asthma)". Chronic lung disease has been described in Africans living with HIV. The participants in this study were young, most had accessed reliable ART for several years, exhibited immune (peripheral CD4 cell)



reconstitution and reliable viral suppression. How should HIV clinicians be monitoring the health of our patient's respiratory tract? Will the COVID19 pandemic require a rethink of our patient's respiratory safety?

Additional reading:

- Desai SR, Nair A, Rylance J, et al. Human immunodeficiency Virus-Associated Chronic Lung Disease in Children and Adolescents in Chest Radiographic and High-Resolution Computed Tomographic Findings. *Clin Infect Dis* 2018; 66(2): 274-81. DOI:10.1093/vid/cix778.
- Shaddock EJ, Richards GA, Murray J. Lung fibrosis in deceased HIV-infected patients with Pneumocystis pneumonia. *S Afr J HIV Med* 2012; 13(2): 64-67

12. Bharuthram N, Feldman C. The diagnostic utility of bone marrow examination in an infectious diseases ward. *SAJHIVMED* 2019/Vol 20, No.1/a974 30 September 2019. <https://doi.org/10.4102/sajhivmed.v20i1.974>

Editor's comment: This is a retrospective review of consecutive bone marrow aspirate and trephine (BMAT) examinations of 327 patients admitted to the Infectious Diseases ward of a large academic hospital in Johannesburg from 2012-2014. Most, n=314 (96%), were PLWH. "What is the utility of BMAT in the context of HIV infection?" A peripheral white blood cell (WBC) cytopenia of $\leq 4 \times 10^9/L$ predicted a "unique" diagnosis (OR 2.38, 95%CI, 1.37-4.14, p = 0.002) and the likelihood of a *mycobacterial* infection (OR 2.11, 95% CI, 1.28-4.41, p = 0.005). "Unique" diagnoses = diagnoses found only on BMAT despite extensive alternate investigation or achieved *before* the results of other tests were available/known. Unique diagnoses occurred in 77 (23.5%) and were *Mycobacterium tuberculosis* (MTB) in 17/77 (22%) and *Mycobacterium avium* complex (MAC) in another 3. Three BMAT's each provided $\geq 1X$ "unique" diagnosis e.g. TB and cancer. Proven or suspected mycobacterial disease accounted for n=57 BMAT's with granulomas, culture-proven *Mycobacterium tuberculosis* without supportive histology in 50, and MTB-confirmed with granulomas in 32. Limitations to this study include its retrospective format, inherent case-selection bias and sadly, the absence of sputum (and urine) MTB rif-resistance gene-Xpert, gene-XPert Ultra and urine LAM (Lipoarabinomannan) support in the arsenal of tools available to the clinician. The latter is particularly disappointing as these molecular diagnostics are currently changing the face of clinical medicine.

13. Mehta UC, van Schalkwyk C, Naidoo P, Ramkissoon A, Mhlongo O, Maharaj NR, Naidoo N, Fieggen K, Urban MF, Krog S, Welte A, Dheda M, Pillay Y, Moran NF. Birth outcomes following antiretroviral exposure during pregnancy: Initial results from a pregnancy exposure registry in South Africa. *S Afr J HIV Med* 2019/Vol 20, No 1/a971/30 September 2019. <https://doi.org/10.4102/sajhivmed.v20i1.971>.

Editor's comment: Recommended reading. Although international first-line ART guidelines have replaced nevirapine (NVP) and efavirenz (EFV), with dolutegravir (DTG), concerns



regarding the safety of ART in pregnancy remain. DTG is teratogenic in the first trimester of pregnancy. Women living with HIV and planning a family and those diagnosed with HIV in the first trimester should not use DTG. This paper addresses the safety of NVP and EFV in pregnancy in a cohort of pregnant SA women.

In 2013, the SA National Department of Health promoted the introduction of a birth-outcomes registry among pregnant women and their infants exposed to ARVs. The authors report on the first 12 months of this programme (2013-2014). Two outcomes were assessed:

(i) **major congenital malformations (CMs)** following ARV exposure *in the first trimester* of pregnancy.

(ii) **adverse birth outcomes (ABOs)** viz. foetal death, preterm delivery, low birth weight, small for gestational age, neonatal death, following ARV exposure *at any time* during pregnancy.

Data were collected at the Prince Mshiyeni Memorial Hospital in Umlazi, Durban, SA. n=10,417 pregnancies and 10, 517 birth outcomes were captured. The overall prevalence of HIV infection was n= 4013/10 417 (38.5%). A higher prevalence was noted in women >35 yr., n=640/1100 (58%) and in multigravida vs. primigravid women, 49.2% vs 21.9% respectively. Numbers of major CMs were small. About a third were in infants of mothers on ART, n=11/27 (29.7%). Compared to uninfected pregnant women unexposed to ARVs, first-trimester exposure to efavirenz in HIV-infected women did not increase the risk of CM, RR 0.87 [95% CI, 0.12-6.4, p=0.895]. However first-trimester nevirapine exposure may increase risk: RR 9.2, 95%CI, 2.27-37.94, p=0.002. This finding may have been influenced by confounders e.g. small numbers and requires more data/confirmation. The risk of ABOs was greater in the infants of mothers with exposure to ART at any time throughout pregnancy vs HIV-uninfected mothers (RR 1.23, 95% CI., 1.14-1.31, p<0.001) but particularly where EFV or NVP-use had started before the pregnancy. This report is published at a time when guidelines are changing. The NNRTIs are being phased out of first-line regimens. But women unable to take DTG are likely to be given EFV or perhaps NVP. This is a high-end paper that is informative and supports the long-term role of EFV in women for whom DTG is contraindicated.*

*Additional reading:

- Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayoudi G, et al. Neural Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Eng J Med. 2019 Aug; 381(9):827-840. doi:10.1056/NEJMoa1905230.
- The National Department of Health, The Republic of South Africa. 2019 Antiretroviral Treatment Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates. October 2019. Dolutegravir Overview, ART Initiation, pg.8. <https://www.health.gov.za>.

October 2019

14. Cele MA, Archary M. Acceptability of short text messages to support treatment adherence among adolescents living with HIV in a rural and urban clinic in KwaZulu-Natal. SAJHIVMED 2019 / Vol 20, No 1 / a976 /03 October 2019. <https://doi.org/10.4102/sajhivmed.v20i1.976>.

Editor's comment: This paper reports the results of a small, questionnaire-based, cross-sectional, pilot study of 100 adolescents (12-19 years) from two clinic sites, one urban (n=50) and the other rural (n=50) in KZN, South Africa. Poor retention in care and unreliable treatment adherence, challenge the success of ART in this group of patients. Will text-messaging remedy the problem? The authors confirm the widespread use (88%) of mobile devices among rural and urban respondents. Though two-thirds were willing to receive messages that provided them with information concerning their health, others were unwilling or undecided. Higher education linked with greater mobile device usage. But who are those – PLWH – who are unwilling or undecided? Did the potential breach of privacy and the risk of unsanctioned disclosure via their smartphone inform the negative response? 48% of the cohort had never sent health-related SMS's to or received (fewer) such messages from their clinic or health-professional. Who are these 12-19 year-olds who are unwilling/undecided? Are these the ones who will be lost to care and fail adherence? How do we ensure these also become confident, understand their rights and are assisted to adhere to ART?

15. Van Wyk B, Davids L-A. Challenges to HIV treatment adherence among adolescents in a low socio-economic setting in Cape Town. SAJHIVMED 2019 /Vol 20, No 1 / a1002 / 28 October 2019. <https://doi.org/10.4102/sajhivmed.v20i1.1002>

Editor's comment: This is a descriptive record of challenges faced by 15 adolescents (10-19 years) living with HIV since birth, and receiving support from a primary care clinic in the greater Cape Town district. The participants were interviewed in 2016 and had been on ART for a minimum of 6 months. Group and individual discussion focused on barriers to and facilitators of adherence. The themes identified by the authors are not new: the conflict between school and clinic, the need for greater "HIV-competency" of households, and the provision of adolescent-friendly health services. Limitations are acknowledged: small numbers, incomplete data saturation, the absence of a wide spectrum of views including that of defaulters. But for me, the strength of the study is in the verbatim comments of the participants. For a brief moment, the reader hears what it is like to be young and stigmatized and shamed by HIV/AIDS. This is why adherence is so difficult. It's not simply a matter of healing our youth, it's rather about society and the ongoing wider response to PLWH.

16. Moodley K, Bill PLA, Patel VB. Motor lumbosacral radiculopathy in HIV-infected patients. SAJHIVMED /Vol 10, No 1/a992/ 28 October 2019. <https://doi.org/10.4102/sajhivmed.v20i1.992>



Editor's comment: This is a short report of 11 young (median age = 29 years) PLWH naïve to ART, who experienced a slowly progressive, bilateral and symmetrical, isolated, lower-motor neurone weakness of the lower limbs. The latter were areflexic and flaccid. The remainder of the neurological examination, including higher function, sensation and sphincter control, were normal. A diagnosis of subacute motor lumbosacral radiculopathy was made. The mean duration of symptoms had been 6.5 months (IQR 3-7.5m). Six were female. Cerebrospinal fluid (CSF) was notable for an elevated protein and the presence of mononuclear cells. Tests for malignancy and various infecting organisms were negative. The group's median CD4 cell count was 327 c/mm³, (IQR, 146-457). Unfortunately, serum and CSF HIV-viral load levels were not drawn. Gadolinium enhancement on magnetic resonance imaging (MRI) was visible in the lumbar ventral roots. Electromyography (EMG) confirmed abnormal activity of the lumbar and lower limb muscles. All the patients were treated for up to 4-6 weeks, with large amounts of oral prednisone (1.5mg/kg/day). Steroids were sometimes given for longer periods. No steroid toxicity and no intercurrent (opportunistic) infection e.g. TB, fungal, was reported. ART was not started immediately and no patient was on ARVs at the time of the diagnosis. 91% recovered within 3.4 months. All except one with mild residual weakness, were 'normal' at the final 18-month follow-up visit. The authors – from the neurology department of the University of KwaZulu Natal (UKZN), Durban, SA - discuss the differential diagnosis and point out that since the rollout in 2017 of "Universal Test and Treat", few additional cases have been seen. **Recommended reading.**

17. Laughton B, Naidoo S, Dobbels EFMT, Boivin MJ, Janse van Rensburg A, Glashoff RH, van Zyl GU, Kruger M, Cotton MF. Neurodevelopment at 11 months after starting antiretroviral therapy within 3 weeks of life. SAJHIVMED 2019/Vol 20, No 1/a1008/30 October 2019 <https://doi.org/10.4102/sajhivmed.v20i1.1008>

Editor's comment. Recommended reading. This is an important, prospective, observational study of 29 infants born to mothers living with HIV (MLWH). All infants were started on ART within 21 days of their birth. Twenty-four of the mothers (n=24/29, 83%) were on ART at the time of delivery. N=23/29 (79%) infants were female. Infant viral load levels at birth had been vl=3904 [median, range 259, 16,022] cp/mL. Viral suppression (vl<400cp/mL) on ART occurred at 19.1 weeks [median, range 15, 36] of age. The Global Griffiths Mental Development Scales (GMDS), an early neurodevelopmental assessment tool, found the infant's developmental scores to be normal at 11.5 ±0.8 months. This was despite the fact that n=9/29 (31%) infants had a detectable bloodstream vl at the time. Of the 5 central nervous system (CNS) domains assessed, locomotor skills scored lowest and hearing and language, the highest. The authors acknowledge that this study is small and their results, preliminary. Nonetheless, these data suggest that ART begun at this extremely young age is safe and beneficial. The authors inform us that a larger study is already underway. This paper is another milestone along the road to beating the virus and to the wellbeing of future generations. Please read it.



18. Archary M, Fairlee L, Slogrove A. Opinion Piece. Current perspectives on paediatric HIV management from the Mexico International AIDS Society Conference, 2019. SAJHIVMED 2019 / Vol 20, No 1 / a1027 / 31 October 2019.
<https://doi.org/10.4102/sajhivmed.v20i1.1027>

Editor's comment: Recommended reading. This is a summary of presentations and discussions held at the following meetings, the 11th International Workshop on Pediatric HIV and the 5th Workshop on Children and Adolescents *HIV-Exposed and Uninfected*, and the International AIDS Society (IAS) Conference in Mexico, July 2019. The authors remark that despite general success in controlling vertical transmission, there were 160,000 new global paediatric HIV-infections in 2018. They add, "subSaharan Africa is struggling with meeting UNAIDS 90-90-90 goals for children and adolescents living with HIV". This is nevertheless an optimistic report that focusses on antiretroviral treatment and the prevention of vertical transmission of HIV.

New antiretrovirals and a new delivery system: **GS-6207**, the first of the **capsid-inhibitor ARV class** but currently no paediatric studies reported. Adult trials are promising. Treatment = long-acting, s/c administration every 3 months. **MK-8591**, the first nucleoside reverse transcriptase **TRANSLOCATION-inhibitor**. No paediatric data but adult studies = prolonged intracellular half-life and low once a week dosing. No cross-resistance to other NRTIs. An adult fixed-dose combination (FDC) in trials: MK-8591+doravirine. A paediatric formulation is possible. **Tenofovir-alafenamide (TAF) in children**, a new NRTI with lower renal and bone demineralisation-risk and a FDC formulation for children aged >6yr and weighing ≥25Kg: TAF/FTC/elvitegravir+cobicistat. Of a variety of novel drug-delivery systems, the adult **transdermal adhesive micro-needle skin patches** that deliver monthly cabotegravir offer new therapeutic/prevention options with potential for paediatric application.

Antiretroviral drug efficacy and safety: Birth defects. The risk of neural tube defects in infants exposed to dolutegravir (DTG) during periconception (first-trimester of pregnancy), appears to be confirmed with updated data from Botswana's Tsepamo Birth Surveillance Study. Nevertheless, the WHO recommends DTG-based ART for all women of child-bearing potential who are living with HIV. Females who are not pregnant must be counselled regarding contraception. And counselling of all women MUST ensure that the decision for either a DTG or EFV-based ART is a fully INFORMED DECISION and decided ahead of the start of ART. Children enrolled in the International Antiretroviral Pregnancy Registry (APR) who had been HIV-exposed yet were uninfected (**CHEU**) had lower birth weight- and length-for-age versus unexposed, uninfected children. Zimbabwe's SHINE study also reported stunting and mortality risk to CHEU. See comment, Metha U, et al. summary 13 above. **Metabolic effects of ART.** Exposure of adults to ART (the South African ADVANCE study) uncovered significant weight gain in all study arms but especially those given both DTG+TAF/FTC. What drug-related-toxicity is emerging and what does this mean for children on these drugs? **Public Health, ART and Children.** Paediatric retention in care and viral load (vl) suppression rates are suboptimal in southern Africa. Adolescent mortality and morbidity risk is too high. 'Children lag-behind' - the International epidemiologic Databases to Evaluate AIDS Southern Africa, leDEA-SA, collaboration data, 2004-2017.



Readers are encouraged to check out this 'Opinion Piece' for themselves. Its background is the success of PMTCT – the prevention of mother-infant HIV transmission. Its reality is the day to day management of young people living with HIV.

19. Dunlop JL, Slemming W, Schnippel K, Makura C, Levin LJ, Rayne S, Vujovic M, Firnhaber C. Breast abnormalities in adolescents receiving antiretroviral therapy. SAJHIVMED 2019/ Vol 20, No 1/a1017/ 06 November 2019.
<https://doi.org/10.4102/sajhivmed.v20i1.1017>

Editor's comment: This is a retrospective report of abnormal breast development in adolescents aged 10-19 years. All were on antiretroviral therapy (ART). The article reflects the January-December 2014 clinic-records of 631 Johannesburg-based adolescents living with HIV (ALWH). n=37/631 (5.9%) had 'abnormal' breasts. Most (n=24/37, 65%) were male (p=0.043). Median duration on ART was 4.9 years. The older adolescents (p<0.0005) and those on efavirenz-based ART (p=0.016) were more likely to have breast problems. 92% (n=34/37) had been on EFV while the remaining 8% were on lamivudine (3TC) monotherapy i.e. were likely to have been on EFV previously. [The prevalence of EFV-use among those with normal breasts – the comparator group - was lower, viz. n=384/594 (74.3%)]. The use of boosted-protease inhibitors such as lopinavir/ritonavir, atazanavir and darunavir, was not associated with breast changes. Although lipodystrophy was recorded in 46.3% and gynecomastia in 29% of those with breast changes, BMI-confirmed over-weight/obesity was found in only 8 (19.5%). More than 70% had viral suppression (vl <50 copies/mL) and immune reconstitution (CD4 count ≥500 cells/mm³). Most of the 37 adolescents took their pills. The file review indicated that clinic physicians 'corrected' the problem by replacing EFV with nevirapine (NVP). This seldom solved the problem. The authors remark, "few were referred for additional breast-care. And of the three who were, none received any definitive intervention." The paper has limitations. Retrospective studies accumulate gaps with time, data gaps. Did the breast abnormalities ever resolve? The use of EFV is widespread in sub-Saharan Africa. Are these toxicities still being seen? Is anyone culpable? After all, these are iatrogenic adverse events. Questions. Perhaps another paper will fill in the gaps?

20. **Guideline.** Govender NP, Meintjes G, Mangena P, Nel J, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med /Vol 20, No 1/a1030/08 November 2019. <https://doi.org/10.4102/sajhivmed.v20i1.1030>.

Editor's comments: I recommend this guideline paper to all. It is a must-read and is up there with the best.

21. **Guideline.** Palliative care guidelines for the management of HIV-infected people in South Africa. Spencer DC, Krause R, Rossouw T, et al. S Afr J HIV Med / Vol 20, No 1/a1013/13 December 2019. <https://doi.org/10.4102/sajhivmed.v20i1.1013>.



Editors comment: My thanks to the colleagues who helped me with this one. If you're interested in this field of HIV medicine please contact the HIV Clinicians' Society. We are eager to start an interest group to develop the field further.

22. **Review.** Kaplan S, Nteso KS, Ford N, Boule A, Meintjes G. Loss to follow-up from antiretroviral therapy clinics: A systematic review and meta-analysis of published studies in South Africa from 2011 to 2015. SAJHIVMED 2019 /Vol 20, No 1 / a984 / 18 December 2019. <https://doi.org/10.4102/sajhivmed.v20i1.984>.

Editor's comment: Recommended reading. This paper provides a meta-analysis of public sector South African ART studies that address loss to follow-up (LTFU) and mortality data. This is an important article and will inform the epidemiology and practice of ART in South Africa in the years ahead.

The data is derived from 48X adult, 15X paediatric and 4X pregnancy studies completed between January 2011 to October 2015. Limitations are acknowledged: non-homogeneous data sources viz. clinics, hospitals, rural and urban sites; and non-standardized definitions of LTFU across sources. When is a client lost to follow-up? After 3 months, 6 months, or 12 months since their last visit? The initiation of ART itself was in flux at the time: baseline CD4 counts varied and treatment varied between private and state providers. Were 'silent transfers' excluded from the LTFU data i.e. clients who move between clinics without informing staff and who are not truly LTFU?

The median cohort study-size was 3737 persons. Median adult age and baseline CD4 count at ART initiation were 35.8 years and 121 cells/mm³ respectively. The median age of ART initiation in children was 4.2 years. The 'defined' follow-up time varied from 9 weeks to 5 years and the meta-analysis indicated no difference in LTFU estimates at 3, 6 or the 12-month census. Overall median mortality at one year was 7.9% (IQR 4.1-11.4; range 0-26%) and the median LTFU at one year, 12.8% (IQR, 7.9-22.0%, range 0.2-43-1%). Aggregate meta-analysis LTFU estimates at one year were 11.6% (95% CI, 11.4-11.7%) in the adult studies, 30.0% (95% CI, 28.7-37.4%) for the pregnant cohorts, and accounted for 7.5% (95% CI, 6.7-8.2%) of the paediatric data. The 5-year LTFU estimate was 25% (95%CI, 24.8-25.4%) based on three adult studies. In their concluding remarks, the authors indicate their support for the standardization of the LTFU definition to 180 days (6 months).

Thank you for reading through this summary of articles published in the Southern African Journal of HIV Medicine August-December 2019. Similar summaries are available for the first half of 2019. If you have suggestions and improvements please contact me at editor@sahivcs.org.

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