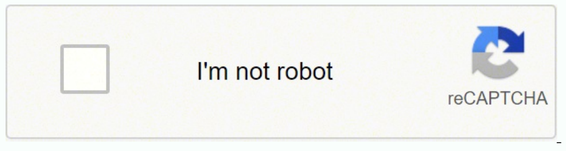

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CASE STUDIES – HIV AND THE KIDNEYS

THE RISKS OF CONCURRENT TREATMENT WITH TENOFOVIR AND AMINOGLYCOSIDES IN PATIENTS WITH HIV-ASSOCIATED TUBERCULOSIS

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The South African public sector antiretroviral treatment (ART) guidelines have recently been changed to include tenofovir in the first-line regimen.[1] Injectable drugs from the aminoglycoside class are part of the intensive phase of regimen 2 tuberculosis (TB) treatment and the multidrug-resistant (MDR) TB treatment regimen (regimen 4). We present two cases that highlight the attention of clinicians managing patients with HIV-associated TB to the potential dangers of concurrent administration of these drugs. We present two illustrative cases.

CASE 1

We recently admitted a 47-year-old man with a background of hypertension who had a serum creatinine level of 131 µmol/l prior to TB. He was diagnosed with pulmonary tuberculosis (*Mycobacterium tuberculosis* was cultured from his sputum). Because he had had a fully treated episode of pulmonary tuberculosis in 2007, he was commenced on regimen 2 TB treatment (including streptomycin during the intensive phase) in March 2010. At this time he tested HIV positive, and because he was CD4 count 28 cells/µl, he was also commenced on lamivudine, lamivudine and efavirenz in May 2010, while still receiving streptomycin. He was referred to our hospital 3 weeks later with a 1-week history of weakness, vomiting and confusion. The creatinine level was now 1 902 µmol/l and the urea level 38 mmol/l. He was admitted, tenofovir was switched to stavudine, streptomycin was stopped, and he received intravenous rehydration and a broad-spectrum antibiotic. His blood and urine cultures were sterile and there was no other evidence of urinary tract infection. His creatinine level steadily decreased and within 3 weeks was 160 µmol/l.

CASE 2

A 28-year-old HIV-infected man was on a lamivudine-based ART regimen when he was diagnosed with MDR TB. He was started on MDR TB treatment including kanamycin and remained on lamivudine. His creatinine level rose from 64 µmol/l to 180 µmol/l within 1 month of starting MDR treatment. He was then referred to our hospital. Tenofovir was changed to stavudine and the kanamycin was stopped, yet his creatinine remained elevated 3 months later (125 µmol/l), suggesting that chronic renal damage may have resulted. He will continue to be followed up.

DISCUSSION

The aminoglycosides are potent nephrotoxins, in part because of the high concentrations they attain in the proximal tubular cells (PTCs) – up to 10% of the total parenteral dose may be concentrated in these cells.[2] They bind to anionic phospholipids in the luminal endoplasmic reticulum, where they can interfere with protein sorting and synthesis,[3] and are then transported into the nucleus and mitochondria where they can inhibit mitochondrial ribosomes[4] (in a way that is analogous to their bactericidal effect on the small ribosomal unit of bacteria). It is thought that one mechanism through which they cause acute tubular necrosis (and Fanconi's syndrome) is tubular mitochondrial toxicity.

Like the aminoglycosides, tenofovir attains high concentrations in the PTCs as a result of active uptake into these cells. A substantial proportion of patients taking tenofovir may develop certain of the features of Fanconi's syndrome (a proximal tubular wasting syndrome) as a result of PTC dysfunction. One study found that 2 – 4% of patients taking tenofovir developed at least 2 out of 6 features of proximal tubular dysfunction such as hyperaminoaciduria, glycosuria in the presence of normoglycaemia, and hypophosphataemia.[5] Tenofovir may also cause renal failure. There is evidence to suggest that tenofovir's nephrotoxicity is related to tubular mitochondrial toxicity with abnormal mitochondria

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Retention in Care Trajectories of HIV-Positive Individuals Participating in a Universal Test-and-Treat Program in Rural South Africa (ANRS 12249 TasP Trial)

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Objective: To study retention in care (RIC) trajectories and associated factors in patients eligible for antiretroviral therapy (ART) in a universal test-and-treat setting (TasP trial, South Africa, 2012–2016).

Design: A cluster-randomized trial whereby individuals identified HIV positive after home-based testing were invited to initiate ART immediately (intervention) or following national guidelines (control).

Methods: Exiting care was defined as ≥3 months late for a clinic appointment, transferring elsewhere, or death. Group-based trajectory modeling was performed to estimate RIC trajectories over 18 months and associated factors in 777 ART-eligible patients.

Results: Four RIC trajectory groups were identified: (1) group 1 "remained" in care (reference, n = 554, 71.3%), (2) group 2 exited care then "returned" after [median (interquartile range)] 4 (3–9) months (n = 40, 5.2%), (3) group 3 "exited care rapidly" [after 4 (4–6) months, n = 98, 12.6%], and (4) group 4 "exited care later" [after 11 (9–13) months, n = 85, 10.9%]. Group 2 patients were less likely to have initiated ART within 1 month and more likely to be male, young (<29 years), without a regular partner, and to have a CD4 count >350 cells/mm^3. Group 3 patients were more likely to be women without social support, newly diagnosed, young, and less likely to have initiated ART within 1 month. Group 4 patients were more likely to be newly diagnosed and aged 39 years or younger.

Conclusions: High CD4 counts at care initiation were not associated with a higher risk of exiting care. Prompt ART initiation and special support for young and newly diagnosed patients with HIV are needed to maximize RIC.

Key Words: universal test and treat, HIV, South Africa, retention in care, trajectories

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INTRODUCTION

South Africa has the highest number of people living with HIV (PLWHIV) in the world, estimated at 7 million in 2015.[1] Forty-nine percent receive antiretroviral therapy (ART), making it the largest treatment program worldwide.[2] Despite a reduction in HIV-related morbidity and mortality and a consequent increase in life expectancy,[3] HIV incidence remains unacceptably high.[4]

In 2016, South Africa adopted the WHO's recommendation to implement a universal test-and-treat (UTT) strategy for HIV.[4] The success of this strategy depends on sustained retention in care (RIC).[5,6] Modeling estimated that to achieve

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Supported by The French National Agency for AIDS and Viral Hepatitis Research (ANRS; grant number, 2011-375) sponsored and cofounded the trial. The Deutsche Gesellschaft fur Internationale Zusammenarbeit (GIZ, grant number, 81151958) and the Bill & Melinda Gates Foundation through the 3ie Initiative cofounded the trial. Merck and Gilead Sciences supported the trial by providing Atripla.

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C.I., J.O.-G., D.P., and F.D. designed and implemented the TasP trial. S.B., C.P., J.L., A.G., and N.M. contributed to the conception and design of the study. A.G. performed the statistical analysis with the support and supervision of S.B. and C.P. A.G. searched the literature, and co-wrote the first draft of the manuscript with S.B. and C.P. All authors contributed to the interpretation and presentation of the findings, revised the article critically for important intellectual content, and approved the final version of the manuscript for submission.

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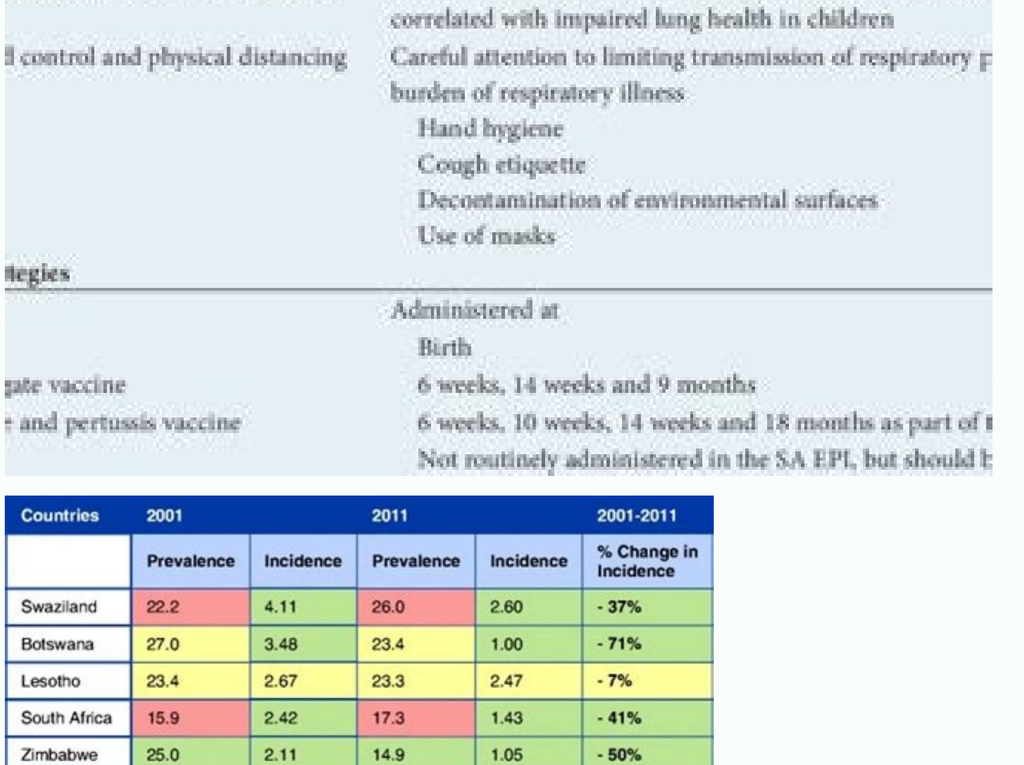
tegies	Summary
	Malnourished children are at increased risk for severe pn
	and mortality
	Breastfeeding is protective
ntation	
	Vitamin A should be dosed according to the Road to Hea
	100 000 IU stat at 6 months; 200 000 IU stat at 12 mon
	at 18 months
	From 24 months onwards, 200 000 IU every 6 months
	Vitamin D-deficient children are at increased risk for CA
	vitamin D 400 IU daily
	Zinc 10 mg (for infants) and 20 mg (for older children) d
	the risk of pneumonia
oking and indoor fuel exposure	Environmental exposure to cigarette smoke or indoor air
	correlated with impaired lung health in children
l control and physical distancing	Careful attention to limiting transmission of respiratory p
	burden of respiratory illness
	Hand hygiene
	Cough etiquette
	Decontamination of environmental surfaces
	Use of masks
tegies	
	Administered at
	Birth
gate vaccine	6 weeks, 14 weeks and 9 months
and pertussis vaccine	6 weeks, 10 weeks, 14 weeks and 18 months as part of t
	Not routinely administered in the SA EPI, but should b

Countries	2001		2011		2001-2011
	Prevalence	Incidence	Prevalence	Incidence	% Change in Incidence
Swaziland	22.2	4.11	26.0	2.60	- 37%
Botswana	27.0	3.48	23.4	1.00	- 71%
Lesotho	23.4	2.67	23.3	2.47	- 7%
South Africa	15.9	2.42	17.3	1.43	- 41%
Zimbabwe	25.0	2.11	14.9	1.05	- 50%
Zambia	14.4	1.89	12.5	0.80	- 58%
Namibia	15.5	2.39	13.4	0.77	- 68%
Mozambique	9.7	1.63	11.3	1.13	- 31%
Malawi	13.8	1.74	10.0	0.49	- 72%



If a maternal HIV test is not feasible, consent should be obtained to perform a rapid HIV test on the child.HIV test at six weeks post-cessation of breastfeedingAge-appropriate HIV testing at six weeks post-cessation of breastfeeding is retained, with emphasis on testing even if breastfeeding continues for longer than 18 months18-month rapid test/ELISA for all children regardless of HIV exposure (universal testing)18-month rapid test for HIV-exposed infantsHIV PCR test used as a confirmatory test for any HIV-positive result up to age two yearsDefinition of high-risk infant exposureMaternal ART for < 4 weeks prior to deliveryHigh-risk infant at birth:Maternal VL ≥ 1000 copies/mL at delivery, or in the last 12 weeks of pregnancyNo maternal VL result available in the last 12 weeksUnknown maternal HIV status because the infant is orphaned or abandonedMaternal VL ≥ 1000 copies/mLHigh-risk infant during breastfeeding (> 72 h after delivery):New maternal HIV diagnosis during breastfeedingMaternal VL ≥ 1000 copies/mL after previous viral suppression on ARTInfant post-exposure prophylaxisHigh-risk infants: AZT for six weeks and NVP prophylaxis for 12 weeksAZT for six weeks and NVP prophylaxis for a minimum of 12 weeks. Exclusive breastfeeding policy, practice and influences in South Africa, 1980 to 2018: A mixed-methods systematic review. Highest risk of mother-to-child transmission of HIV or death in the first 6 months postpartum: Results from 18-month follow-up of an HIV-exposed national cohort, South Africa [homepage on the Internet]. If the maternal VL is not suppressed by 12 weeks, continued NVP is given until maternal VL suppression is achieved, or until four weeks after breastfeeding cessation.BreastfeedingBreastfeeding recommended for 12 months (later changed to 24 months)Breastfeeding recommended for 24 months or longer whilst ensuring maternal ART and viral suppression, in line with recommendations for the general population. Lancet. Durban: Health Systems Trust; 2016. 2019;14(10):e0224029. Fogel J, Li Q, Taha TE, et al. Myer L, Phillips TK. Pediatric HIV: Progress on prevention, treatment, and cure. Goga A, Jackson C. 1. 2019;16(9):e1002895 10.1371/journal.pmed.1002895 [PMC free article] [PubMed] [CrossRef] [Google Scholar]25. Moyo F, Haeri Mazanderani A, Barron P, et al. Lancet HIV. JAIDS; 2017;75(1):S115–S122. 10.1097/qad.0000000000000212 [PubMed] [CrossRef] [Google Scholar]3. HIV Med; 2016;18(2):80–88. New Engl J Med. 2018;37(6):559–563. 2019;38(5):508–512. Zash R, Holmes L, Diseko M, et al. Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomised trial (DolPHIN-1 study). Nieuwoudt SJ, Ngandu CB, Manderson L, Norris SA. 10.1097/qai.0000000000001343 [PubMed] [CrossRef] [Google Scholar]28. 10.1097/qai.0000000000000501 [PMC free article] [PubMed] [CrossRef] [Google Scholar]13. 10.1089/aid.2015.0366 [PubMed] [CrossRef] [Google Scholar]30. Available from: [Google Scholar]16. Predictors of perinatal HIV transmission among women without prior

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Gertsch A, Michel O, Locatelli I, et al. 10.1093/cid/cir008 [PMC free article] [PubMed] [CrossRef] [Google Scholar]Page 2Summary of the main changes in the South African 2019 prevention of mother-to-child guideline.Contents2015 consolidated HIV guideline2019 PMTCT guidelineOverall approach-A renewed focus on the practicality for the end userAn operational focus on the integration of services, provision of a one-stop service, linkages to care, including care provided in the community by community health workers and other relevant stakeholdersPrevention-Guidance on universal infection precautions, and for preventing HIV acquisition in HIV-negative women and sero-discordant couplesPlanned pregnancies and safe conception-Guidance for family planning and contraception in WLWH, as well as on safer conceptionMaternal HIV testingAt first visit, at 32 weeks, and every three months during breastfeedingAt first visit and at every subsequent BANC visit, and three-monthly during breastfeedingMaternal ART-Guidance on adherence messagesGuidance for the use of DTG in women of childbearing potentialMaternal HIV VL monitoring Guidelines for newly diagnosed mothers, and WLWH already on ARTAdditional guidance for previously ART-exposed mothersVL done at delivery and at six months post-partum for all women, and six-monthly during breastfeedingART for the mother presenting in labour Stat dose NVP and TDF/FTC, and AZT three-hourly during labourStat dose of NVP and a stat dose of TDF, 3TC, and DTG in a fixed-dose combination (TLD)Start ART next day (TLD preferred), after appropriate counsellingInfant HIV testing HIV PCR test at birth and 10 weeksHIV PCR test at birth and 10 weeks remain unchanged18-week HIV PCR test for high-risk infants removedSix-month HIV PCR test for all HIV-exposed infants introduced18-week PCR test for high-risk infants who received extended NVP for 12 weeksAt six months of age, establish the HIV status of all infants not already known to be HIV-exposed by offering an HIV test to the mother. 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