Polypharmacy and drug-drug interactions in low-income and middle-income countries

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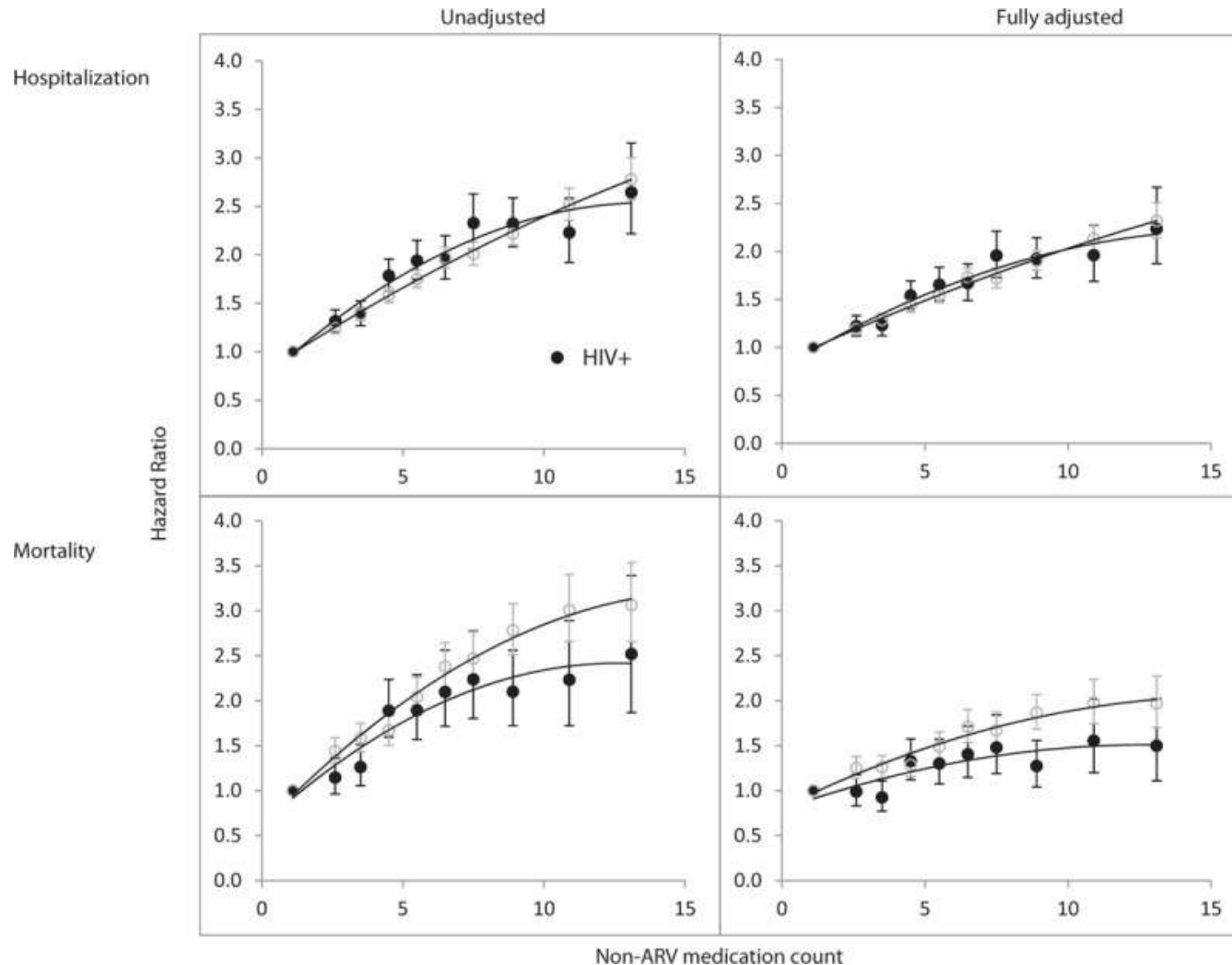Investing In The Future – Impacting Real Lives

Nonantiretroviral polypharmacy and adverse health outcomes among HIV-infected and uninfected individuals

**US Based Study**
9473 HIV+ and
39 812 uninfected individuals

Increasing risk of hospitalization and mortality when HIV+ and HIV-ve patients exposed to increasing counts of non-ART medication

Risk factors older age, hypertension, diabetes, cardiovascular disease, pain, psychiatric disorders, GERD...

Justice AC et al. AIDS. 2018 Mar 27; 32(6): 739–749.
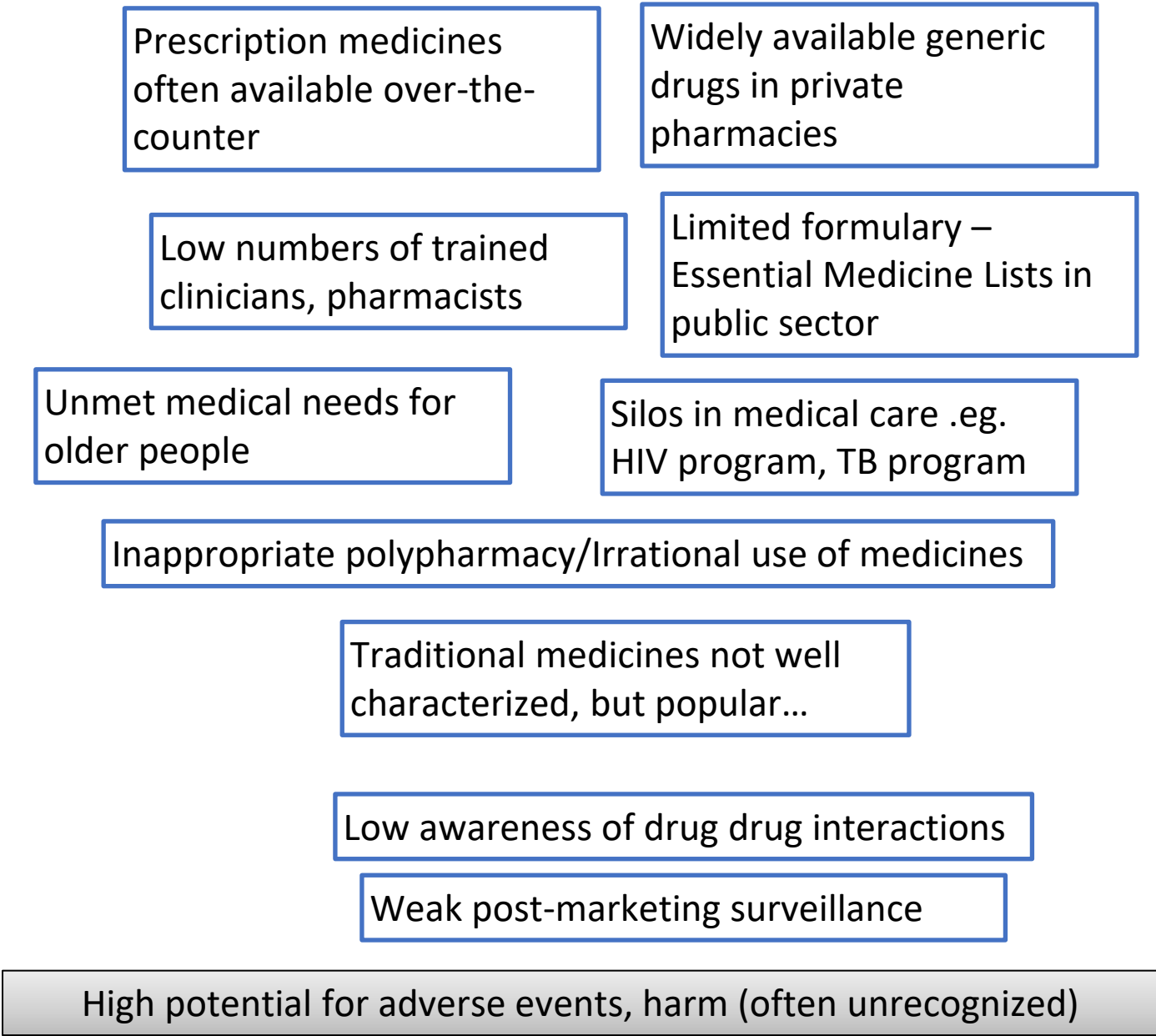Edelmen EJ. Drugs Aging. 2013 Aug;30(8):613-28
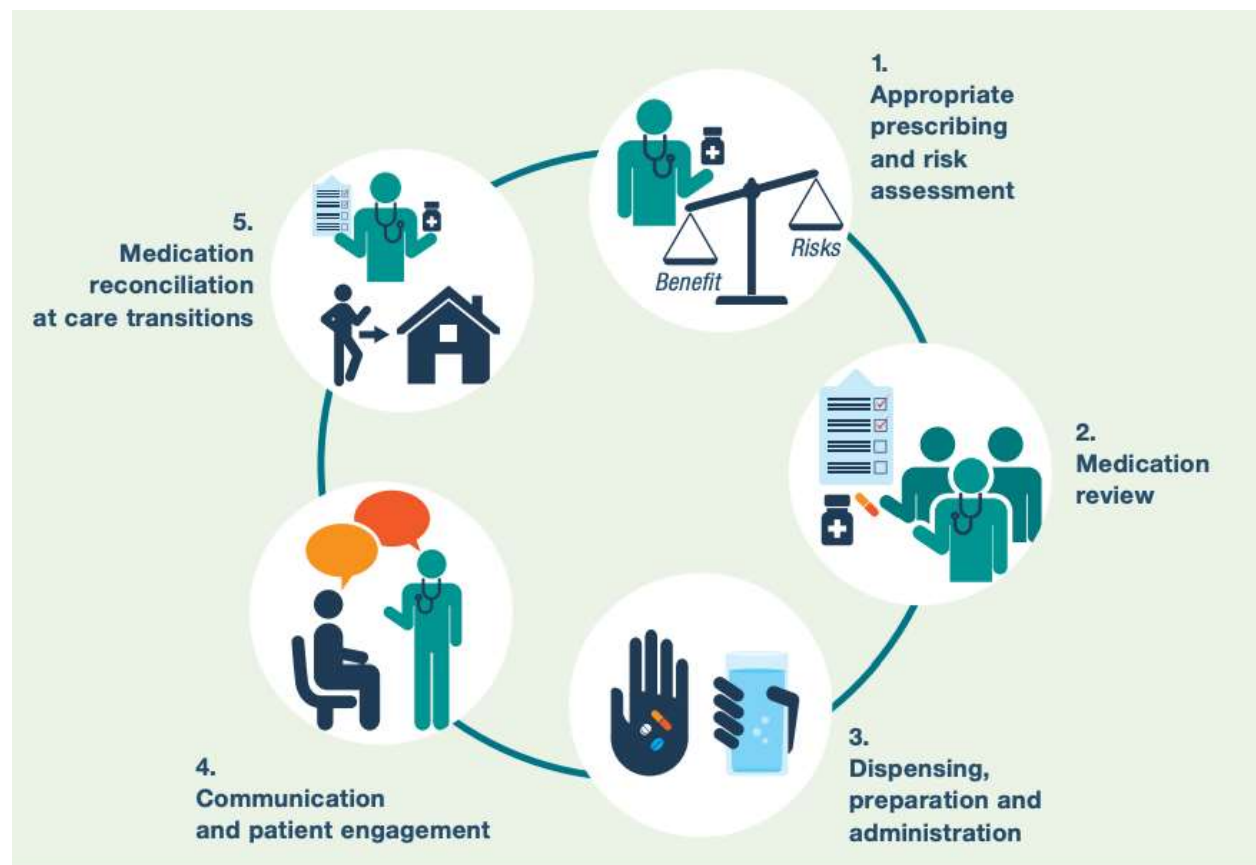
Prescribing indicators at primary health care centers within the WHO African region: a systematic analysis (1995–2015)

	Prescribing indicators		
	Average number of medicines prescribed per encounter[a]	Percentage of medicines prescribed by generic name	Percentage of encounters[b] with an antibiotic prescribed
WHO reference values [12, 13]	<2	100 %	<30 %
Facility type			
All	3.1 (IQR 2.3–4.8)	68.0 % (IQR 55.4–80.3)	46.8 % (IQR 33.7–62.8)
	n = 138,671	n = 121,797	n = 120,422
Public[a]	2.6 (IQR 2.2–4.7)	68.9 % (IQR 57.6–84.5)	45.0 % (IQR 30.1–60.2)
	n = 44,596	n = 28,046	n = 26,071
Private[a]	2.5 (IQR 2.3–3.2)	61.3 % (IQR 47.7–75.7)	51.3 % (IQR 37.5–66.6)
	n = 92,475	n = 92,151	n = 92,751

Ofori-Asenso, R.,. *BMC Public Health* **16,** 724 (2016).
https://doi.org/10.1186/s12889-016-3428-8

Polypharmacy - concurrent use of multiple medications

1. **Over-the-counter drugs**
2. **Prescription drugs**
3. **Traditional and complementary medicines**

CONSIDERATIONS IN LOW- and MIDDLE-INCOME COUNTRIES

Prescription medicines often available over-the-counter

Widely available generic drugs in private pharmacies

Low numbers of trained clinicians, pharmacists

Limited formulary – Essential Medicine Lists in public sector

Unmet medical needs for older people

Silos in medical care .eg. HIV program, TB program

Inappropriate polypharmacy/Irrational use of medicines

Traditional medicines not well characterized, but popular...

Low awareness of drug drug interactions

Weak post-marketing surveillance

High potential for adverse events, harm (often unrecognized)

Ofori Asenso Pharmacy (Basel). 2016 Dec; 4(4): 35.

HIV: Common clinical scenarios requiring polypharmacy

Infectious comorbidities - HIV, tuberculosis, cryptococcal meningitis, malaria, other opportunitistc infections and malignancies

- **Advanced HIV (late presentation)[1]**

- **Diagnostic uncertainty, delayed diagnosis**

Advancing age and multimorbidity

- **Non-communicable diseases - hypertension, diabetes, stroke**

- **Health system gaps - Unment medical needs (eg. surgery, geriatric medicine)**

  - **Only 5/93 patients > 60 years had normal scores on physical function assessment in HIV clinic in Kampala[2]**

1. Kiragga A. BMC Infect Dis 2019 Jan 21;19(1):77.   2. Lwanga et al. AIDS Care. 2020 Nov;32(11):1467-1470

Polypharmacy among HIV positive older adults on anti-retroviral therapy attending an urban clinic in Uganda

METHODS: Cross sectional study in older adults (>50 years) on ART in an outpatient clinic, interviewed and assessed for polypharmacy (≥ 4 non- HIV medications) and frailty.

- Of 411 participants, 63 (15.3, 95% C.I. 11.9, 18.8) had polypharmacy
- In multivariate analyses, polypharmacy was associated with
  - \> or = 1 hospitalisations in the last year (PR = 1.8, 95% C.I. 1.1, 3.1, p = 0.02),
  - prescription by an internist (PR = 3.6, 95% C.I. 1.3, 10.5, p = 0.02)
  - frailty index scores of 5 to 6 (PR = 10.6, 95% C.I. 1.4, 78, p = 0.02)

Participants with Polypharmacy

Most commonly used medicine classes ($n = 289$ total different medicines used among 63 participants with polypharmacy)

Drug Class	n (%)
Antihypertensive agents	72 (24.9)
Diuretics	48 (16.6)
Non-steroidal anti-inflammatory agents	17 (5.9)
B group vitamins and minerals	16 (5.5)
Beta-adrenergic blocking agents	13 (4.5)
Hyperacidity, reflux and ulcers	12 (4.2)
General well-being, multiple use preparations like herbs, others	10 (3.5)
Antidepressants	9 (3.1)
Hypoglycaemic agents	9 (3.1)
Simple analgesics and antipyretics	8 (2.8)

Prevalence of DDI in context of HIV

> **Prevalence and type of drug–drug interactions involving ART in patients attending a specialist HIV outpatient clinic in Kampala, Uganda**
>
> K. Seden[1]*, C. Merry[2,3], R. Hewson[1], M. Siccardi[1], M. Lamorde[2,3], P. Byakika-Kibwika[2,3], E. Laker[2],

METHODS

- 2000 patients receiving ARVs in Kampala.

- Most recent prescription screened for clinically significant DDIs using www. hiv-druginteractions.org.

- Logistic regression were used to identify risk factors for DDIs.

- A screening tool was developed using significant risk factors and tested in a further 500 patients.

RESULTS

- 374 patients (18.7%) of patient had a total of 514 DDIs
- Common: antibiotics [20%], antifungals (16.9%] and antihelminthics [15.8%]
- 4 contraindications – nevirapine + ketoconazole

Logistic regression analysis of patient factors contributing to risk of DDIs

variable	OR (95% CI)	P
At least two comedications	3.4 (2.3–5.1)	<0.0001
Second-line (PI-containing) regimen	2.8 (1.9–4.1)	<0.0001
WHO stage 3–4	1.4 (1.0–1.9)	0.04
Anti-infective	11.5 (8.4–15.7)	<0.0001

Seden et al. Antimicrob Chemother 2015; 70: 3317–3322

Prevalence and nature of potential drug-drug interactions among hospitalized HIV patients presenting with suspected meningitis in Uganda

Methods: 3 cryptococcal meningitis trials between 2010 and 2017 in Kampala, Uganda, medications received over hospitalization were documented and potential DDI events were assessed.
IBM Micromedex DRUGDEX®
HIV-drug-druginteractions.org

RESULTS: Prevalence of all potential DDIs = 89.3% (ART related: 30.9% of overall potential DDI events)

Mean frequency of 4.27 potential DDIs per patient.

Classification: 11.3% contraindicated, 66.4% major, 17.4% moderate and 5% minor potential DDIs were observed.

Most prevalent drugs - fluconazole (58.4%), co-trimoxazole (25.7%), efavirenz (15.6%) and rifampin (10.2%).

Eneh et al. BMC Infectious Diseases (2020) 20:572

Severity[a]	Drug 1	Drug 2	% pDDI overall[b]	Level of evidence[c]	Proposed effect summary
Contraindicated					
	Fluconazole	Ondansetron	3.6	Fair	Risk of QT interval prolongation
	Fluconazole	Haloperidol	2.8	Fair	Increased haloperidol exposure, risk of QT interval prolongation
	Fluconazole	Ritonavir	1.1	Fair	Increased ritonavir exposure, risk of QT interval prolongation
	Artane	Potassium (oral)	0.8	Fair	Gastrointestinal lesions
	Fluconazole	Atazanavir	0.8	Fair	Increased atazanavir exposure, risk of QT interval prolongation
	Fluconazole	Artemether-lumefantrine	0.7	Fair	Risk of QT interval prolongation
	Dihydroartemisinin-piperaquine	Efavirenz	0.2	Fair	Risk of QT interval prolongation
	Fluconazole	Dihydroartemisinin-piperaquine	0.2	Fair	Risk of QT interval prolongation
	Haloperidol	Metoclopramide	0.2	Fair	Increased extrapyramidal reactions and neuroleptic malignant syndrome
	Fluconazole	Quinine	0.1	Fair	Increased quinine levels, risk of QT interval prolongation

Malaria

Co-administered drug	Effect on artemether-lumefantrine exposure		
	artemether	DHA	lumefantrine
rifampicin[1]	89% ⬇	85% ⬇	68% ⬇
nevirapine[2]	72% ⬇	37% ⬇	21% ⬇
efavirenz[2]	77% ⬇	75% ⬇	55% ⬇
LPV/r[3]	43% ⬇	Not affected ⬇	386 ⬆

Simulations suggest artemether-lumefantrine dose increases required[4]
- 250% dose increase with efavirenz
- 75% dose increase with nevirapine

[1]Lamorde et al AIDS 2013 [2]Byakika-Kibwika et al JAC 2012 [3]Byakika-Kibwika JAC 2012 [4]Hoglund BJCP 2014

Review: ART versus artemisinin derivatives. Kiang et al. Clin Pharmacokinet. 2014

Dolutegravir plus antimalarials

A) Pooled Dolutegravir concentrations
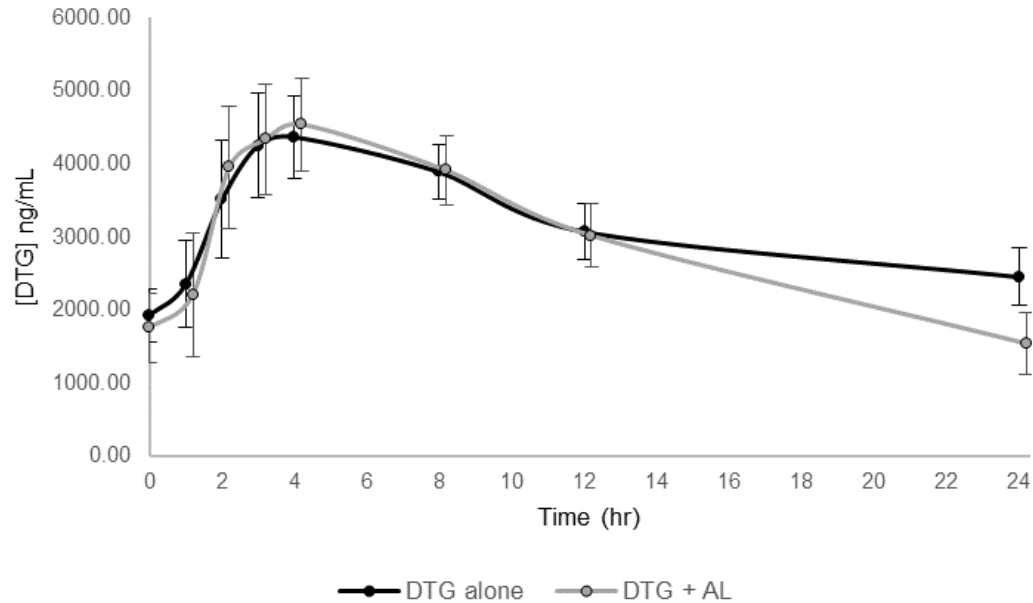
A) Pooled Dolutegravir concentrations
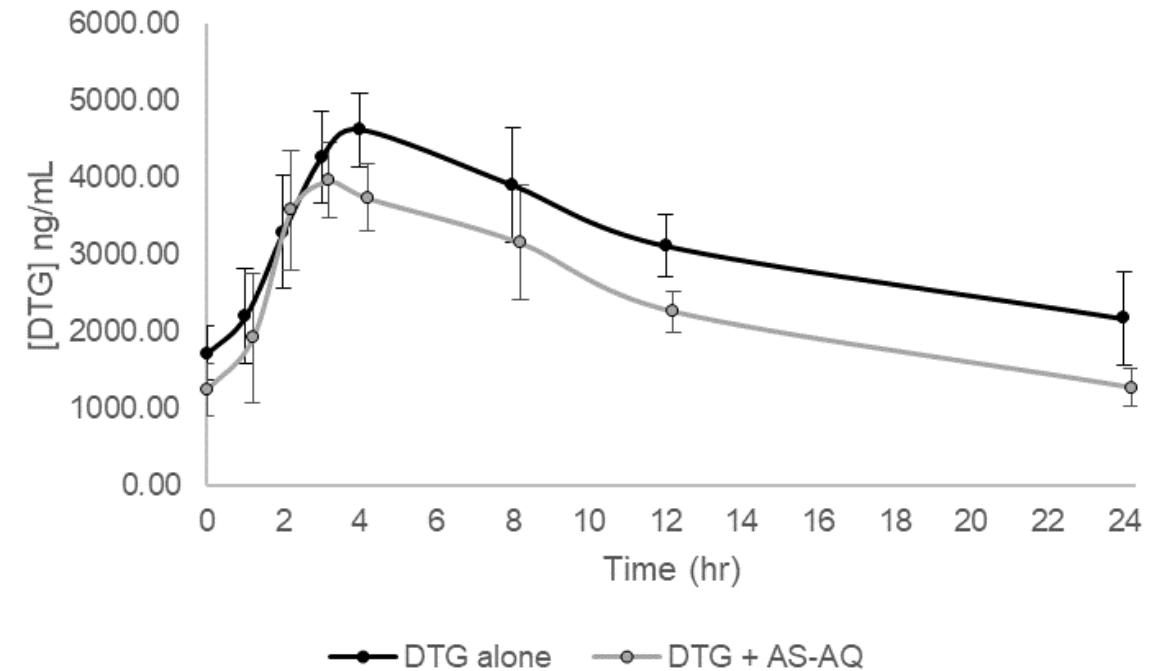
- Dolutegravir can be used at standard doses with artemether lumefantrine (AL) and artesunate amodiaquine (AS-AQ)

PK of First-Line Tuberculosis Drugs in TB/HIV Co-Infection

A Systematic Review on the Effect of HIV Infection on the Pharmacokinetics of First-Line Tuberculosis Drugs

Daskapan. Clin Pharmacokinet. 2019; 58(6): 747–766.
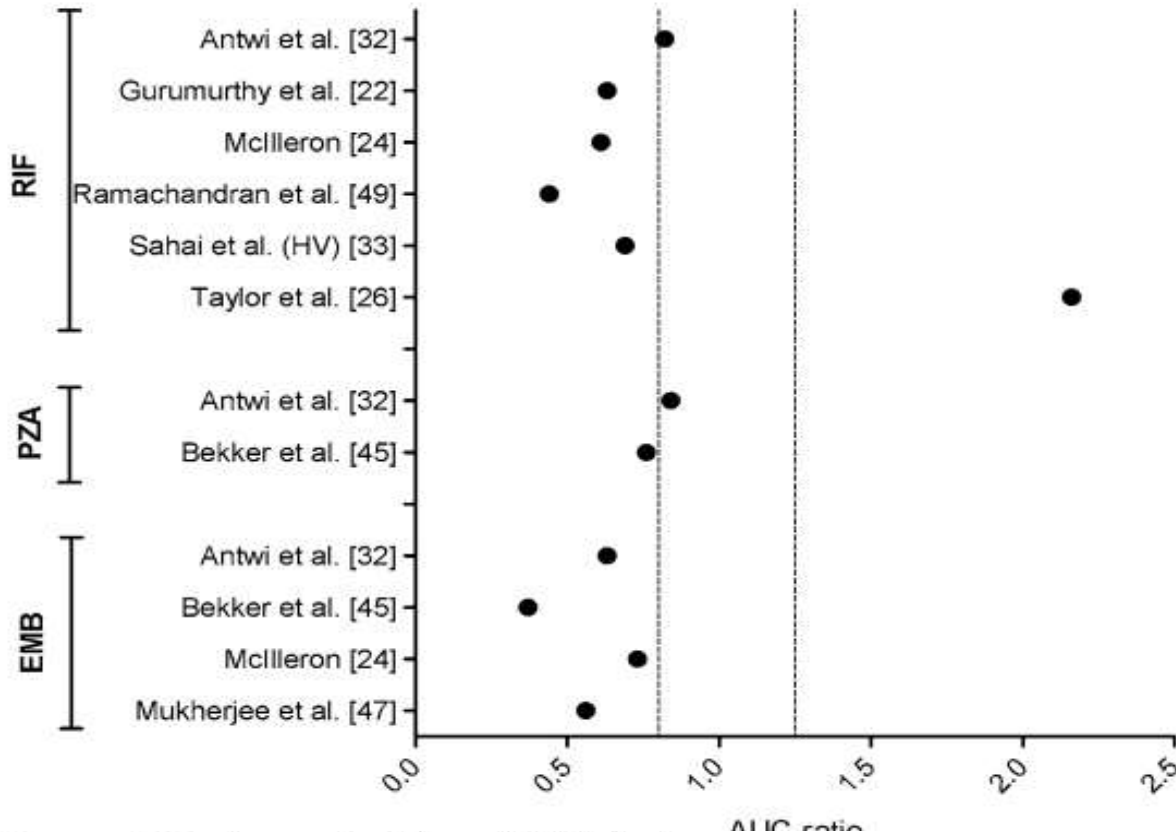
Comparison of simulated exposures using the current dosing strategy versus the suggested dose increment
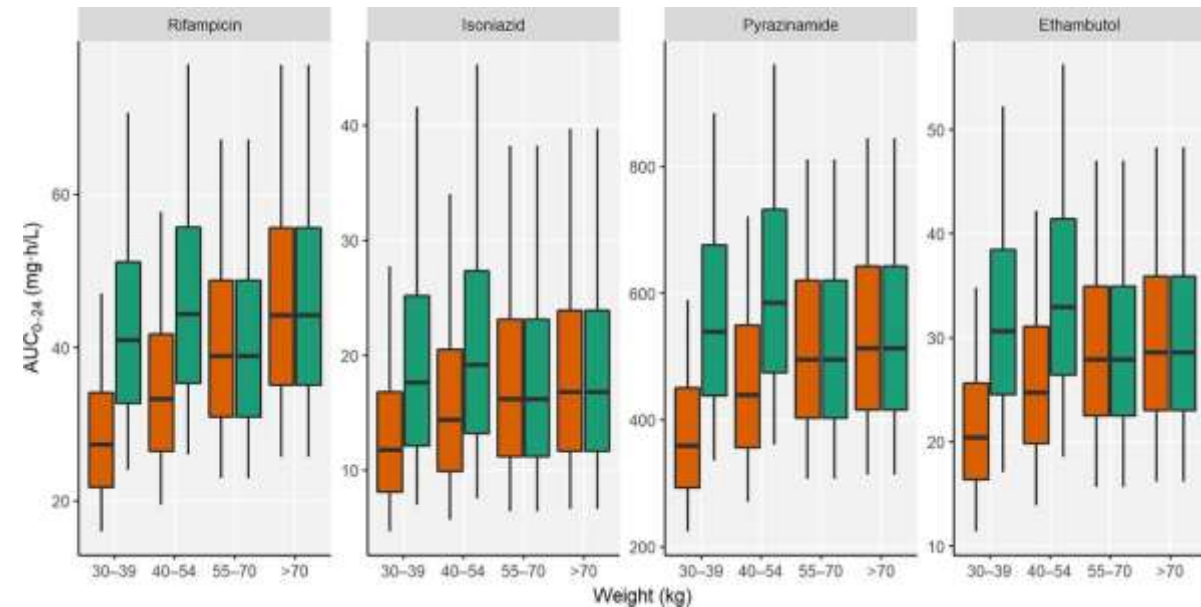
Low Antituberculosis Drug Concentrations in HIV-Tuberculosis Coinfected Adults with Low Body Weight: Is It Time To Update Dosing Guidelines?

Christine Sekaggya-Wiltshire et al. Antimicrob. Agents Chemother. 2019

Medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in Uganda

Mohammed Lamorde[a,b,*], John R.S. Tabuti[c], Celestino Obua[d], Collins Kukunda-Byobona[e], Hindam Lanyero[d], Pauline Byakika-Kibwika[a,b,f], Godfrey S. Bbosa[d], Aloysius Lubega[d], Jasper Ogwal-Okeng[d], Mairin Ryan[b], Paul J. Waako[d], Concepta Merry[a,b,f,g]

- 103 plant species were reported by 25 traditional medicine practitioners

- Decoctions use of multiple plants to make a single remedy

- 1 in 5 traditional medicine practitioners treated children

Neglected Tropical Diseases

Interactions between ART and NTD drugs

Evidence for all recommendations: low quality or very low quality

Seden et al. AIDS 2013

3TC, lamivudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; d4T, stavudine; ddl, didanosine; DRV/r, darunavir/ritonavir; EFV, efavirenz; Entry-I, entry inhibitor; ETV, etravirine; FPV/r, fosamprenavir/ritonavir; FTC, emtricitabine; IDV, indinavir; Int-I, integrase inhibitor; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NFV, nelfinavir; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PIs, protease inhibitors; RAL, raltegravir; Ril, rilpivirine; RTV, ritonavir; SQV/r, saquinavir/ritonavir; TDF, tenofovir; TPV/r, tipranavir/ritonavir; ZDV, zidovudine. ● No clinically significant interaction expected. ■ Potential interaction — may require close monitoring, alteration of drug dosage or timing of administration. ● These drugs should not be coadministered. Quality of Evidence [12], 1. High. 2. Moderate. 3. Low. 4. Very Low.

Ongoing projects

HASA

Senior Fellow: Dr Barbara Castelnuovo

Diagnosis and treatment of non-communicable diseases and geriatric syndromes in the HIV ageing population in sub-Saharan Africa

Infectious Diseases Institute Limited (IDI), Kampala, Uganda
Starting date: 1 April 2019
Duration: 60 months
Grant agreement: TMA2017GSF-1936