

Ecological risk assessment of antiretroviral drugs

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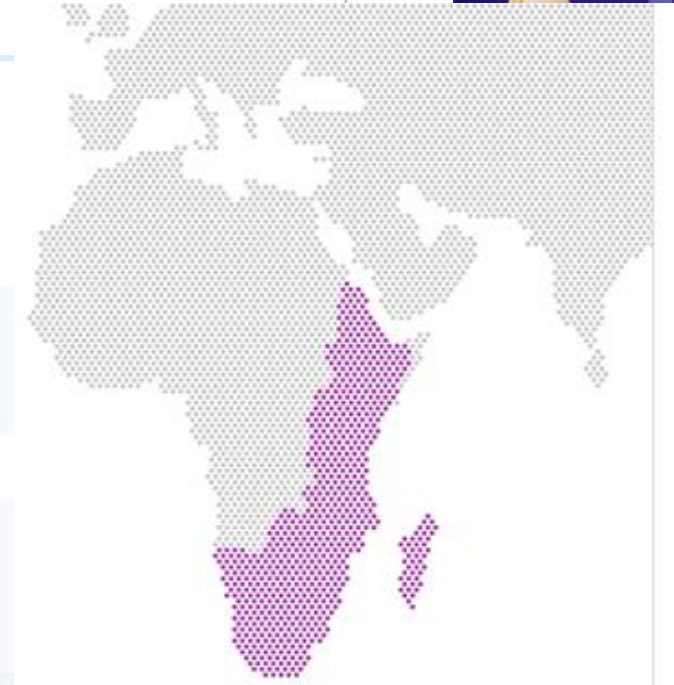
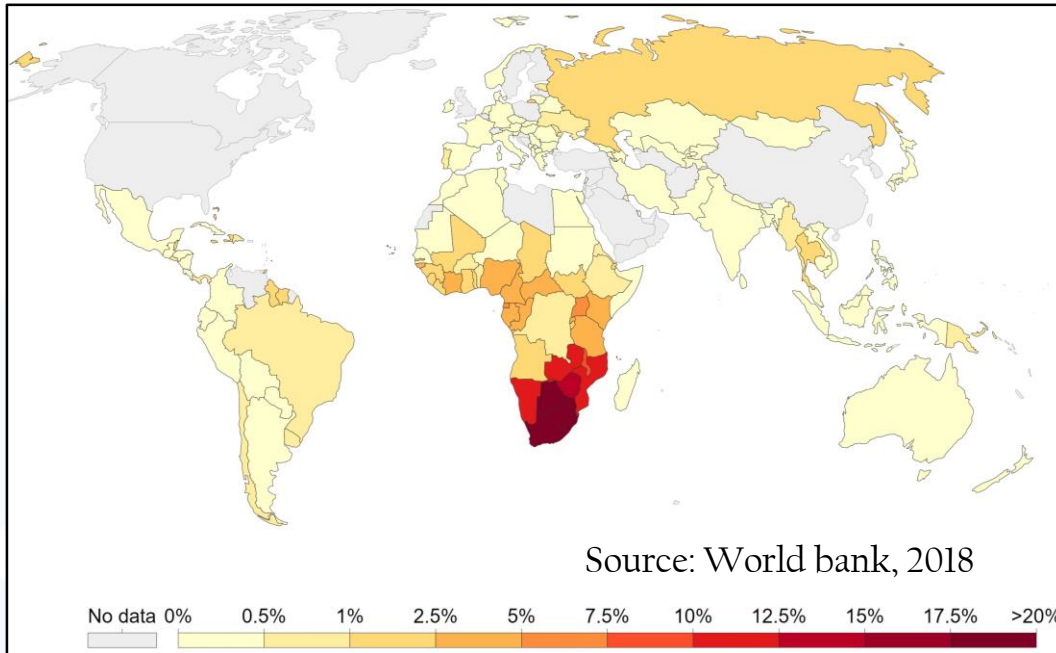
Emerging Contaminants Ecology and Risk
assessment (ECERA) Group

Sustainable Development Goals: focus on health

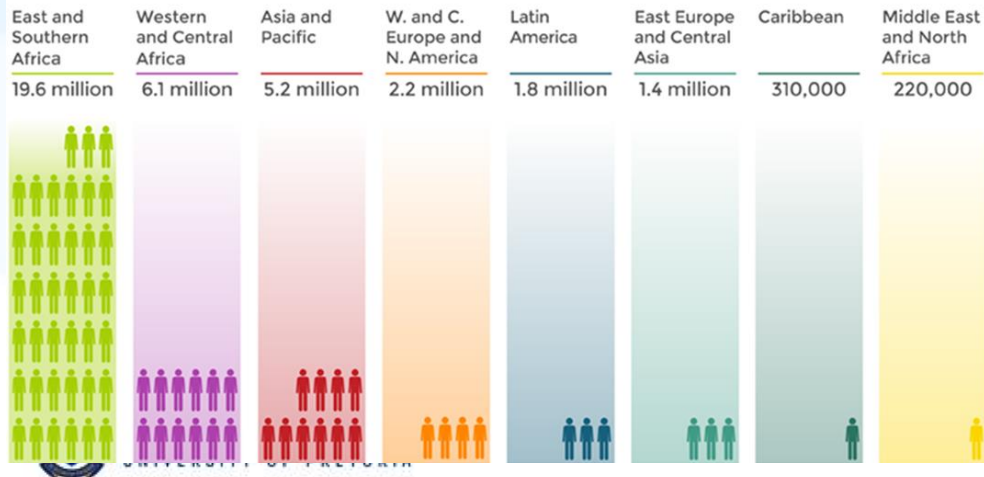


- End the epidemics of HIV/AIDS by 2030
- 36.9 million people globally were living with HIV in 2017
- 21.7 million – accessing antiretroviral therapy (ART) in 2017
- 1.8 million – new infections in 2017
- 940 000 deaths from AIDS – related illnesses in 2017
- 77.3 million infections since the start of the epidemic

Prevalence of HIV: global, and SSA



Number of people living with HIV in 2017



Source: UNAIDS Data 2018

East and Southern Africa (2018)

20.6m people living with HIV

7% adult HIV prevalence (ages 15-49)

800,000 new HIV infections

310,000 AIDS-related deaths

67% adults on antiretroviral treatment*

62% children on antiretroviral treatment*

*All adults/children living with HIV

Source: UNAIDS Data 2019



Table 1

Approved antiretroviral drugs in the USA and Europe.

Generic name	Brand name	Manufacturer	Date of FDA approval
Zidovudine	Retrovir	GlaxoSmithKline	19 March 1987
Didanosine	Videx (tablet)	Bristol-Myers Squibb	9 October 1991
	Videx EC (capsule)	Bristol-Myers Squibb	31 October 2000
Zalcitabine	Hivid	Hoffmann-La Roche	19 June 1992
Stavudine	Zerit	Bristol-Myers Squibb	24 June 1994
Lamivudine	Epivir	GlaxoSmithKline	17 November 1995
Saquinavir	Invirase (hard gel capsule)	Hoffmann-La Roche	6 December 1995
	Fortovase (soft gel capsule)	Hoffmann-La Roche	7 November 1997
Ritonavir	Norvir	Abbott Laboratories	1 March 1996
Indinavir	Crixivan	Merck	13 March 1996
Nevirapine	Viramune	Boehringer Ingelheim	21 June 1996
Nelfinavir	Viracept	Agouron Pharmaceuticals	14 March 1997
Delavirdine	Rescriptor	Pfizer	4 April 1997
Efavirenz	Sustiva (USA)	Bristol-Myers Squibb	17 September 1998
	Stocrin (Europe)	Merck	17 September 1998
Abacavir	Ziagen	GlaxoSmithKline	17 December 1998
Amprenavir	Agenerase	GlaxoSmithKline	15 April 1999
Lopinavir + ritonavir	Kaletra	Abbott Laboratories	15 September 2000
	Aluvia (developing world)	Abbott Laboratories	15 September 2000
Tenofovir disoproxil fumarate (TDF)	Viread	Gilead Sciences	26 October 2001
Enfuvirtide	Fuzeon	Hoffmann-La Roche & Trimeris	13 March 2003
Atazanavir	Reyataz	Bristol-Myers Squibb	20 June 2003
Emtricitabine	Emtriva	Gilead Sciences	2 July 2003
Fosamprenavir	Lexiva (USA)	GlaxoSmithKline	20 October 2003
	Telzir (Europe)	GlaxoSmithKline	20 October 2003
Tipranavir	Aptivus	Boehringer Ingelheim	22 June 2005
Darunavir	Prezista	Tibotec, Inc.	23 June 2006
Maraviroc	Celsentri (Europe)	Pfizer	18 September 2007
	Selzentry (USA)	Pfizer	18 September 2007
Raltegravir	Isentress	Merck & Co., Inc.	12 October 2007
Etravirine	Intelence	Tibotec Therapeutics	18 January 2008
Fixed dose drug combinations			
Lamivudine and zidovudine	Combivir	GlaxoSmithKline	27 September 1997
Abacavir, zidovudine and lamivudine	Trizivir	GlaxoSmithKline	14 November 2000
Abacavir and lamivudine	Epzicom (USA)	GlaxoSmithKline	2 August 2004
	Kivexa (Europe)	GlaxoSmithKline	2 August 2004
TDF and emtricitabine	Tivicay	Gilead Sciences	2 August 2004
Efavirenz, emtricitabine and TDF	Atripla	Bristol-Myers Squibb & Gilead Sciences	12 July 2006

'85-
'89

1987

Zidovudine (NRTI)

'90-
'94

1991

Didanosine (NRTI)

1992

Zalcitabine (NRTI)

1994

Stavudine (NRTI)

'95-
'99

1995

Lamivudine (NRTI)
Saquinavir (PI)

1996

Indinavir (PI)
Nevirapine (NNRTI)
Ritonavir (PI)

1997

Combivir (FDC)
Delavirdine (NNRTI)
Nelfinavir (PI)

1998

Abacavir (NRTI)
Efavirenz (NNRTI)

1999

Amprenavir (PI)

'00-
'04

2000

Didanosine EC (NRTI)
Kaletra (FDC)
Trizivir (FDC)

2001

Tenofovir DF (NRTI)

2003

Atazanavir (PI)
Emtricitabine (NRTI)
Enfuvirtide (FI)
Fosamprenavir (PI)

2004

Epzicom (FDC)
Truvada (FDC)

'05-
'09

2005

Tipranavir (PI)

2006

Atripla (FDC)
Darunavir (PI)

2007

Maraviroc (CA)
Raltegravir (INSTI)

2008

Etravirine (NNRTI)

'10-
'14

2011

Complera (FDC)
Nevirapine XR (NRTI)
Rilpivirine (NNRTI)

2012

Stribild (FDC)

2013

Dolutegravir (INSTI)

2014

Cobicistat (PE)
Elvitegravir (INSTI)
Triumeq (FDC)

'15-
'19

2015

Evotaz (FDC)
Genvoya (FDC)
Prezcobix (FDC)

2016

Descovy (FDC)
Odefsey (FDC)

2017

Juluca (FDC)

2018

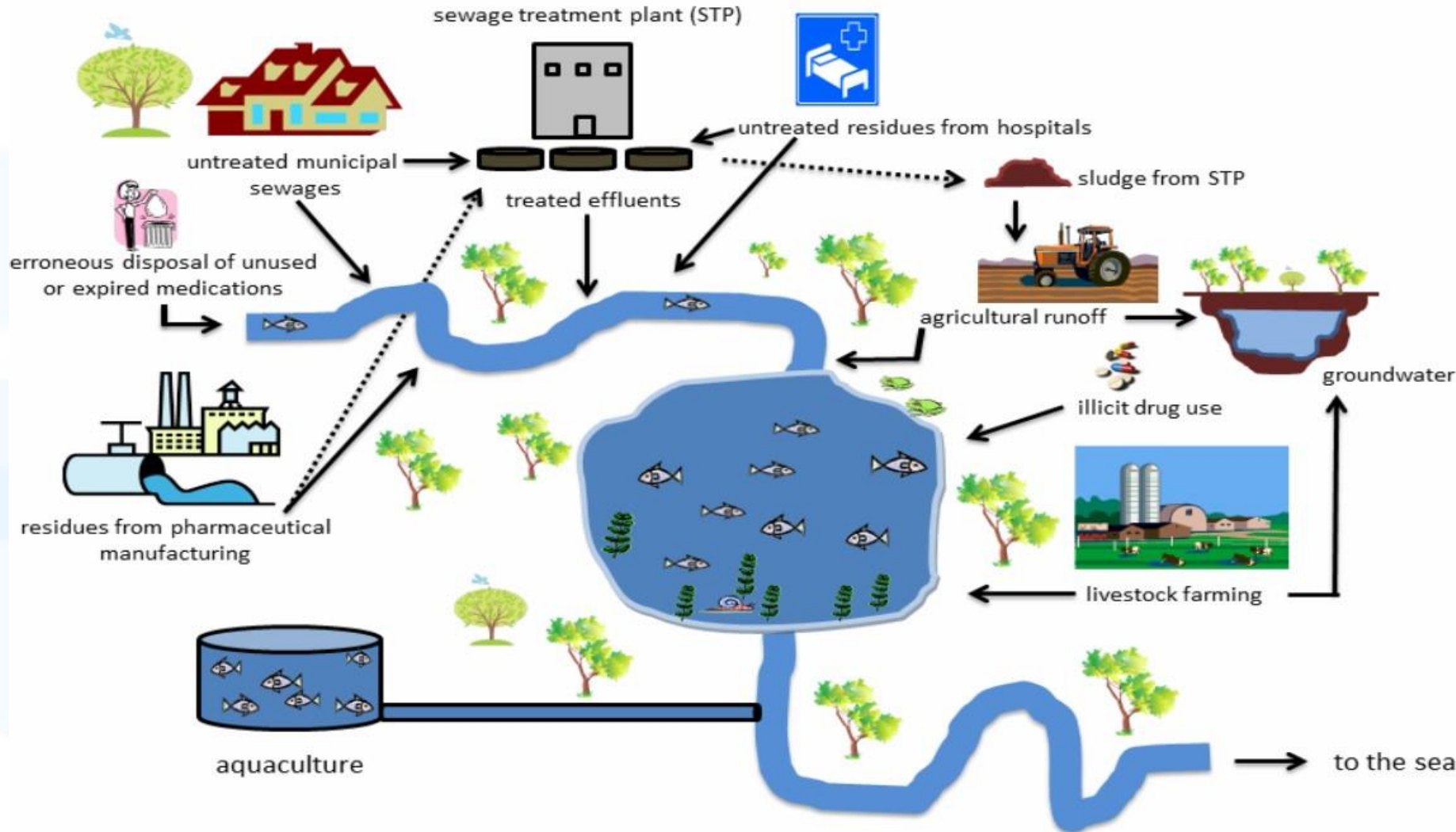
Biktarvy (FDC)
Cimduo (FDC)
Delstrigo (FDC)
Doravirine (NNRTI)
Ibalizumab-uiyk (PAI)
Symfi (FDC)
Symfi Lo (FDC)
Symtuza (FDC)
Temixys (FDC)

2019

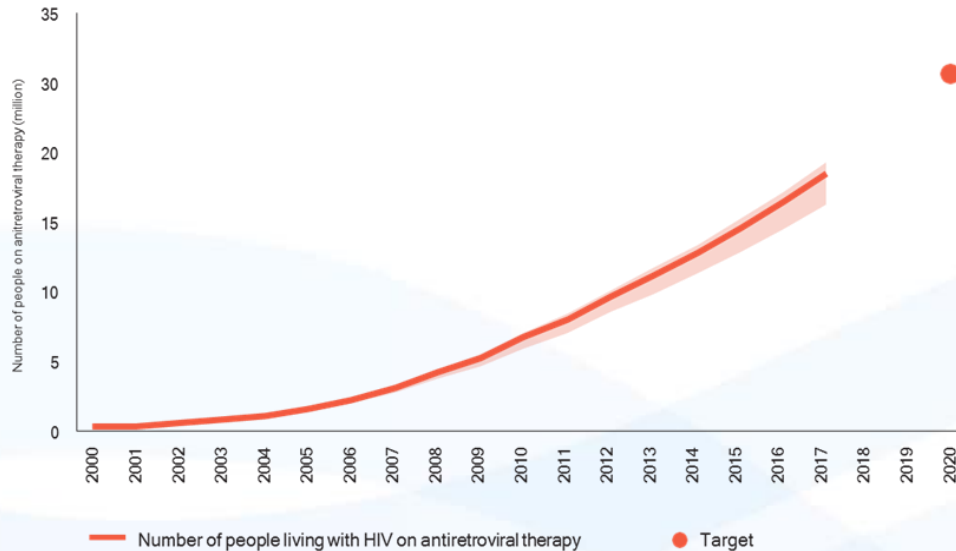
Dovato (FDC)



Sources of ARVs to the environment

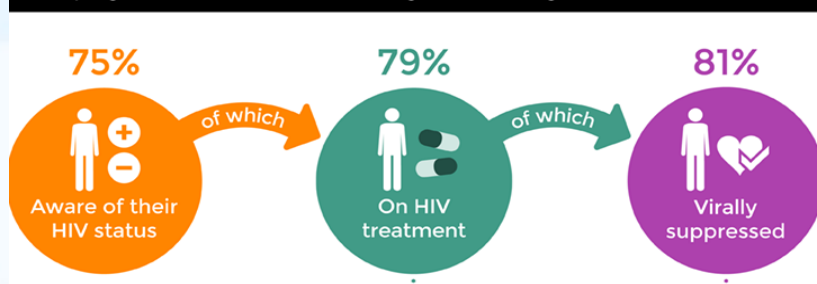


Presence of ARVs in the environment



Source: UNAIDS 2018 estimates. Global AIDS Monitoring, 2018.

Global progress towards the 90 90 90 targets 2017 (all ages)



- “treatment for all” (WHO, 2017)
- “90–90–90”: 2020 treatment target

Antivirals	Conc. (µg/L)	Location	Source
Ribavirin	0.02	South Africa	WWTP influent
Famciclovir	0.00004	South Africa	WWTP effluent
	0.02	South Africa	WWTP influent
	0.00006	South Africa	WWTP effluent
Tenofovir	0.25	South Africa	Surface water
Zalcitabine	0.07	South Africa	Surface water
	0.008	South Africa	Tap water
Lamivudine	0.09 – 0.24	South Africa	Surface water
Didanosine	0.05	South Africa	Surface water
Stavudine	0.41 – 0.78	South Africa	Surface water
	0.102 – 0.778	Kenya	Surface water
Zidovudine	0.07	South Africa	Tap water
	0.0183	Kenya	Surface water
Nevirapine	0.24 – 1.48	South Africa	Surface water
Efavirenz	17.4	South Africa	WWTP influent

Why ARVs of ecological concern?



- Increased prescription of lifelong ART has led to consequent release of antiretrovirals (ARVs) into the environment
- E.g. ~ 20 tons of ARVs are consumed every day globally: SA ~ 5 tons/d (Ncube et al., 2018)
- Societal and medical benefits of ARVs, for example: rapid reduction in mortality, improved quality of life, and dramatic reduction in loss of productive years ... BUT **ecological risks remain unquantified**

Organism	Antiviral	No. of studies
Bacteria	Zidovudine	1
	Stavudine	1
Algae	Stavudine	1
Daphnia	Stavudine	1
Fish	Nevirapine	3
	Efiverenz	1
	Rest	0

Effects of ARVs on aquatic organisms



Antivirals	Organism	Duration	Results
Nevirapine	Fish	30 d	No significant detrimental effects on fish growth
Nevirapine	Fish	30 d	No adverse effects on larvae hatching, survival and behaviour
Nevirapine	Fish	60 d	Low growth rate compared to the control
Efavirenz	Fish	96 h	Liver damage and overall decline in fish health
Zidovudine	Bacteria	30 min	No growth inhibition
Stavudine	Bacteria	2 h	DNA damage increased with increasing UV doses
	Algae	72 h	TPs inhibited algal growth
	Crustacean	48 h	No immobility

Ecological Structure Activity Relationship (ECOSAR) Model for Predicting Toxicity



- Computer program that uses chemical structure to predict toxicity of a chemical to aquatic organisms based on the quantitative structure activity relationships (QSARs)
- QSAR data are submitted by industries under Toxic Substances Control Act (TSCA) or collected from publicly available sources
 - Acute and chronic toxicity endpoints
 - Fish, aquatic invertebrates, and algae
- High Concern: acute value $< 1 \text{ mg/L (ppm)}$
chronic $< 0.1 \text{ mg/L}$
- Low Concern: chronic $> 10.0 \text{ mg/L (EPA 2012)}$

Toxicity of ARVs derived using the ECOSAR model



Antivirals	Acute toxicity (mg/) (E/LC50)			Chronic toxicity (CHV mg/l)		
	Algae (96h)	D magna (48h)	Fish (96h)	D Magna	Algae	Fish
Abacavir	10.4	3.71	54.6	0.044	3.3	0.642
Emtricitabine	7 820	3 320	47 300	163	1 770	13 900
Lamivudine	7 930	3 320	47 700	162	1 790	14 300
Zidovudine	0.02	114	411	30.3	0.0055	2.83
Didanosine	37.1	1470	22 300	25	12.9	4.89
Efavirenz	1.51	0.725	0.996	0.141	0.686	0.13
Etravirine	2.51	1.37	2.24	0.02	0.296	0.0098
Nevirapine	0.6	1.81	2.48	0.602	0.884	0.074
Lopinavir	0.027	0.0075	0.099	0.0047	0.011	0.0045
Nelfinavir	0.034	0.093	0.52	0.011	0.015	0.0087
Ritonavir	0.023	0.0041	0.062	0.0031	0.0096	0.0029
Enfuvirtide	—	—	—	—	—	—

Risk assessment of ARVs in the environment



- Entails 3 steps
 - exposure assessment
 - hazard assessment, and
 - risk characterization

$$RQ = \frac{MEC}{PNEC}$$

- $RQ > 1$ indicates high risk to the aquatic community
- $RQ < 1$ indicates medium or no risk MEC

Risk assessment results...



Country	ARV type	FW MEC (ng/L)	Max MEC (ug/L)	PNEC (ug/L)	RQ
Kenya	Nevirapine	30-5 620	5.62	0.0074	759
South Africa	Nevirapine	130-1 480	1.48	0.0074	200
Kenya	Efavirenz	560	0.56	0.013	43
Kenya	Zidovudine	40-17 410	17.41	0.00055	31 655
South Africa	Zidovudine	51.7-973	0.97	0.00055	1 769
Kenya	Zidovudine	9 000	9.00	0.00055	16 364
Kenya	Zidovudine	18 300	18.30	0.00055	33 273
Kenya	Zidovudine	17 410	17.41	0.00055	31 655
Kenya	Zidovudine	7 700	7.70	0.00055	14 000
South Africa	Tenofovir	145-243	0.24	0.248	1
South Africa	Zalcitabine	8.4-71.3	0.07	4.72	<1
South Africa	Lamivudine	94.5-242	0.242	16.2	<1

Concluding remarks...



- Generated data contribute towards systematic risk assessment of ARVs in the environment, and form basis for development of science evidence – based policy, and legislative frameworks to support their responsible, and sustainable use without compromising ecological integrity
- ECOSAR model suggests some ARVs may be highly toxic to aquatic organisms, hence toxicity assessment of ARVs is URGENTLY required
- Preliminary model results on estimated risks of ARVs in freshwaters suggest certain ARV types pose potentially severely/significantly high risk to aquatic organisms (e.g. algae, daphnia, and fish)

Future perspectives



- Need for monitoring programs and legislative guidelines globally for ARVs in ecological systems including in South Africa
- Systematic assessment of potential ARV risks to ecological systems both for parent and transformation products in different environmental compartments – and likely links to human health
- Adoption of multidisciplinary approach (draw expertise from numerous fields of specializations)
- Development of roadmap with defined milestones for immediate-, medium-, and long-term intervention mechanisms to undertake systematic risk assessment of ARVs

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