Antiretroviral Drugs in African Surface Waters: Prevalence, Analysis, and Potential Remediation

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ABSTRACT

The sources, ecotoxicological impact, and potential remediation strategies of antiretroviral drugs (ARVDs) as emerging contaminants in surface waters are reviewed based on recent literature. The occurrence of ARVDs in water bodies raises concern because many communities in Africa depend on rivers for water resources. Southern Africa is a potential hotspot regarding ARVD contamination due to relatively high therapeutic application and detection thereof in water bodies. Efavirenz and nevirapine are the most persistent in effluents and are prevalent in surface water based on environmental concentrations. Whereas the highest concentration of efavirenz reported in Kenya was 12.4 μg L^{-1}, concentrations as high as 119 and 140 μg L^{-1} have been reported in Zambia and South Africa, respectively. Concentrations of ARVDs ranging from 670 to 34 000 ng L^{-1} (influents) and 540 to 34 000 ng L^{-1} (effluents) were determined in wastewater treatment plants in South Africa, compared with Europe, where reported concentrations range from less than limit of detection (LOD) to 32 ng L^{-1} (influents) and less than LOD to 22 ng L^{-1} (effluents). The present African-based review suggests the need for comprehensive toxicological and risk assessment of these emerging pollutants in Africa, with the intent of averting environmental hazards and the development of sustainable remediation strategies.

Keywords: Antiretroviral drugs; Africa; Emerging chemical pollutants; Remediation; Wastewater treatment; Water pollution

INTRODUCTION

Human immunodeficiency virus/autoimmune deficiency (HIV/AIDS) has caused >15 million deaths in Africa, according to the report of the Joint United Nations Programme on HIV/AIDS (2020), and the viral infection has raised major public health concerns and attracted global attention. Africa holds >15% of the world's population, and reports indicate that two-thirds of the global population living with HIV/AIDS are residents of Sub-Saharan Africa (Buvé et al. 2002; World Health Organization 2019). There are countries with very successful antiretroviral therapy programs, in terms of the percentage of infected people on antiretroviral treatment, for example, Australia (90%), Sweden and Botswana (both 83%), Rwanda, Italy, Cambodia, and Switzerland (80% each; Joint United Nations Programme on HIV/AIDS 2020). Other countries with ≥70% of its infected population on antiretroviral treatment programs as of 2019 were Swaziland (79%), France (78%), Spain and Ireland

(77%), Algeria (76%), Zimbabwe (75%), and South Africa (70%; World Health Organization 2019; Joint United Nations Programme on HIV/AIDS 2020). In South Africa, 62% of approximately 7.7 million people living with HIV had commenced antiretroviral treatment therapy as of 2018 (Joint United Nations Programme on HIV/AIDS 2020). Swaziland (now Eswatini) has had the highest HIV/AIDS prevalence and reports the most successful antiretroviral treatment program (Joint United Nations Programme on HIV/AIDS 2020). The countries in Africa with the highest number of people living with HIV and on HIV-antiretroviral treatment are shown in Figures 1 and 2. However, most countries provide treatment programs to individuals with an inadequate immune system, which is currently measured as a CD4 count of ≤350/cells mm^{-3} in adults, and thus these statistics may not present the full picture of the number of HIV/AIDS patients in those countries (Van Damme et al. 2006; World Health Organization 2019). Based on this information, there have been enormous governmental and nongovernmental efforts toward implementing a wider coverage of antiretroviral treatment programs (Table 1).

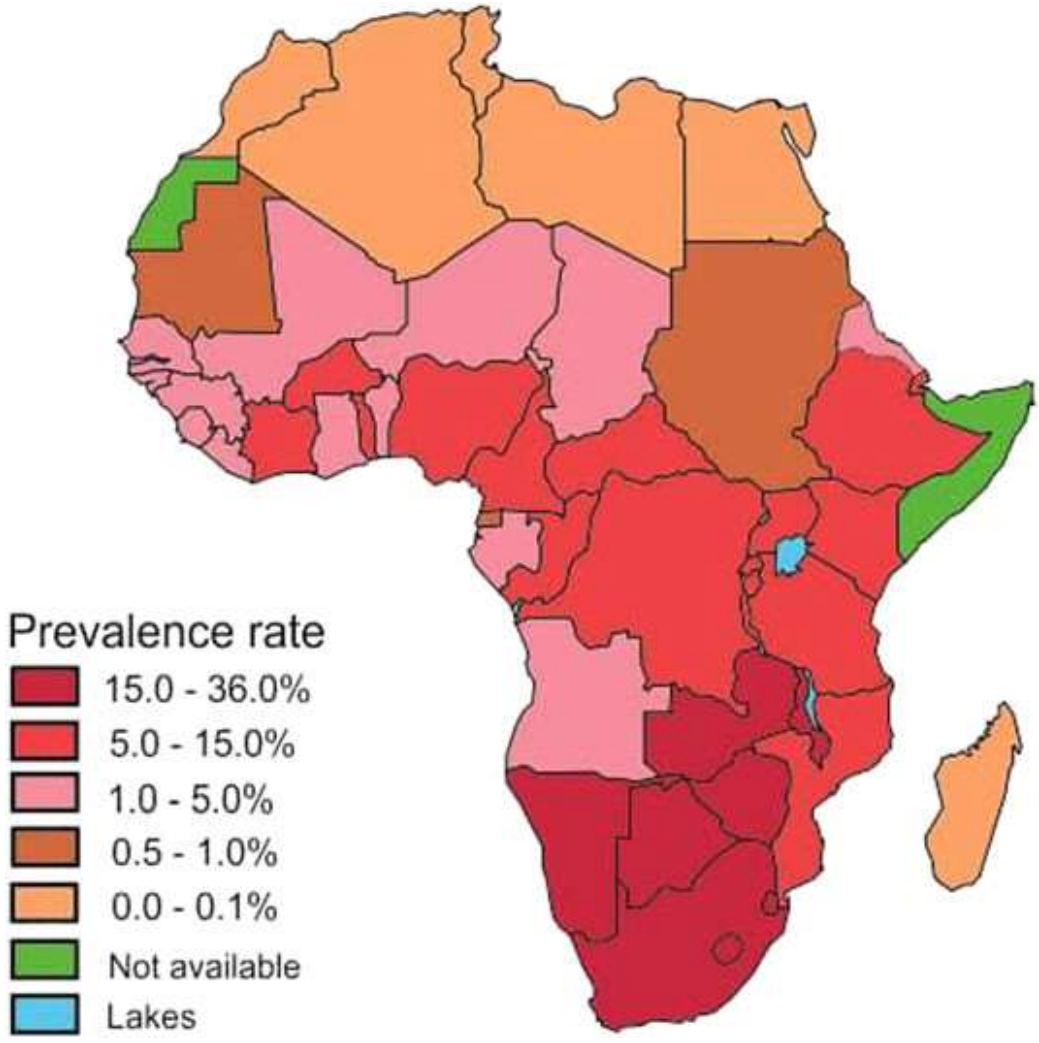

Figure 1: Countries in Africa with a fast-growing number of people on antiretroviral drug treatment (Dwyer-Lindgren et al. 2019; Joint United Nations Programme on HIV/AIDS 2020).

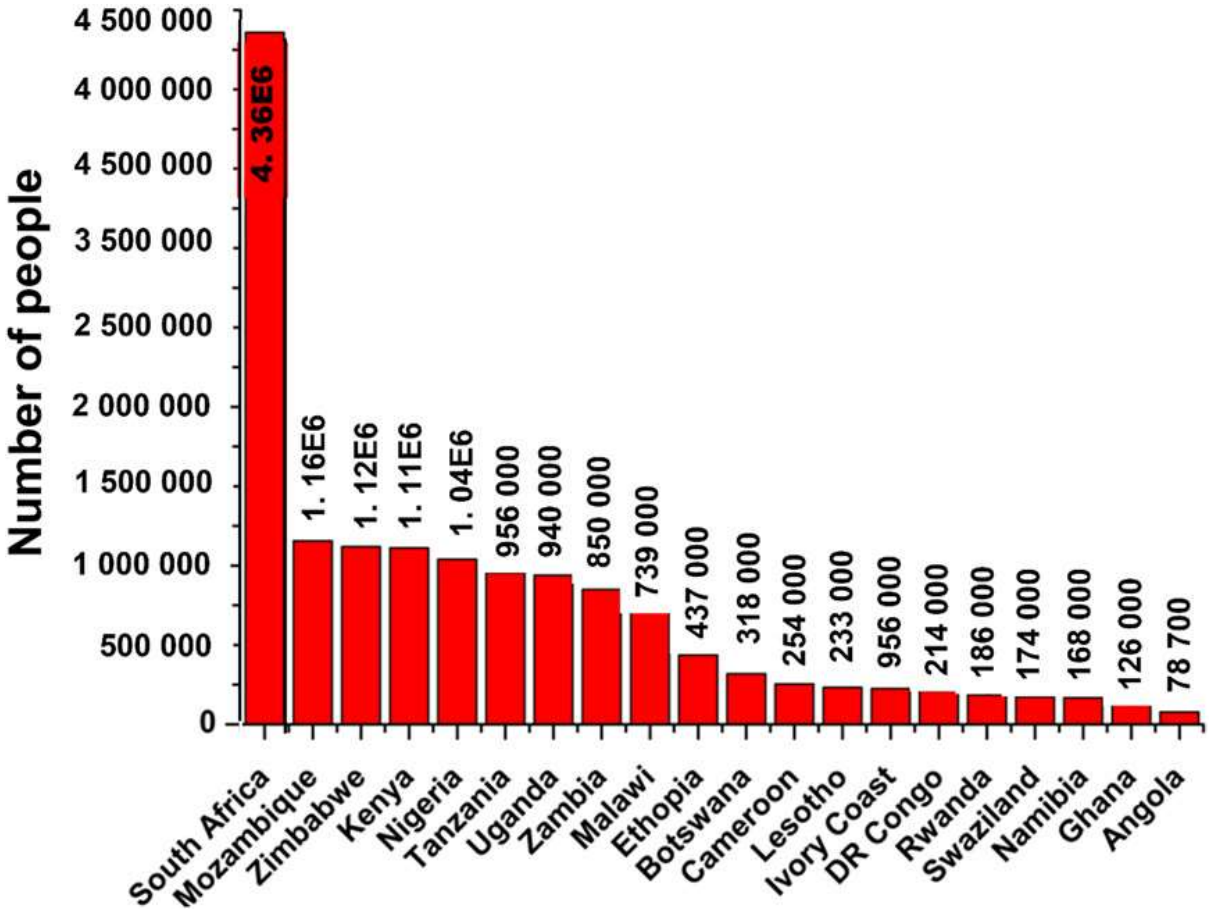

Figure 2: Top 20 countries in Africa with the highest number of people on HIV antiretroviral treatment therapy (World Health Organization 2019).

TABLE 1: Antiretroviral therapy coverage and data for the Southern African Development Community[a]

S/N	Country	Estimated antiretroviral therapy coverage (%)	Estimated no. of people receiving antiretroviral therapy	Estimated no. of people living with HIV
1.	Angola	23–33	93 310	290 000–410 000
2.	Botswana	74–89	313 850	340 000–410 000
3.	Comoros	32–100	77	<100–<500
4.	DR Congo	43–65	277 592	420 000–640 000
5.	Eswatini	88–100	191 782	190 000–220 000
6.	Lesotho	61–70	220 828	320 000–360 000
7.	Madagascar	11–17	5166	32 000–49 000
8.	Malawi	71–84	832 908	960 000–1 100 000
9.	Mauritius	22–29	2837	9700–13 000
10.	Mozambique	48–74	1 338 100	1 800 000–2 800 000
11.	Namibia	79–91	177 174	190 000–220 000
12.	Seychelles	No data	No data	No data
13.	South Africa	64–74	5 231 809	6 900 000–8 000 000
14.	Tanzania	67–81	1 277 012	1 500 000–1 800 000
15.	Zambia	80–92	1 064 321	1 200 000–1 300 000
16.	Zimbabwe	74–97	1 149 191	1 200 000–1 600 000

[a]Data from World Health Organization (2019).

Antiretroviral drugs (ARVDs) are therapeutic agents for the treatment of retroviral infections such as HIV-1, also popularly called the HIV disease. The HIV-1 virus infects the CD4 T cells responsible for the body's immunity. Antiretroviral treatment against HIV-1 does not eliminate the virus but rather prevents its rapid replication (Ncube et al. 2018). The ARVDs as well as other pharmaceuticals are emerging contaminants that are ultimately discharged

into water bodies. Approximately 90% of orally administered drugs are passed out as fecal waste into sewage systems, either unaltered or in partially metabolized forms (Halling-Sørensen et al. 1998; Tambosi et al. 2010). Unused drugs and expired drugs are often disposed of indiscriminately and therefore get into drainage systems and ultimately reach waterbodies (Abafe et al. 2018). Potential hotspot reservoirs of ARVDs include wastewaters, on-site sanitation systems, leachates from nonengineered landfills, shallow groundwater systems, and surface waters. There are growing environmental concerns about the pollution potential of ARVDs as a result of the increasing number of people on treatment programs (Table 1).

Antiviral drugs are classified into 2 broad groups, namely, ARVDs, and non-ARVDs (Tyring 2004). Antiretroviral drugs are used to treat retroviruses, which are different from other viruses based on the mode of replication within their host, which involves RNA genetic materials and not DNA materials like other viruses. Over half of the antiviral drugs are antiretroviral, and ARVDs are further classified based on their mode of action, such as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, fusion inhibitors, postattachment inhibitors, integrase inhibitors, pharmacokinetic enhancers, and so on. The US Food and Drug Administration has approved >20 ARVDs, and many more are in clinical trials (Swati et al. 2011; Jain et al. 2013; Chahal et al. 2017). Non-ARVDs used for the treatment of virus infections include nucleoside analogs like acyclovir, famciclovir, ganciclovir, valacyclovir, penciclovir, ribavirin, and valganciclovir (Tyring 2004). Other ARVDs widely used in HIV treatment therapy in Africa include nevirapine and efavirenz; their structures are shown in Figure 3.

Emerging chemical pollutants are substances that are yet to be classified as priority pollutants, and thus they are not routinely monitored (Geissen et al. 2015). However, due to their toxicity, persistence, and/or detection in various environmental compartments, they are chemical pollutants of emerging concern and will potentially attract future legislation against illicit or indiscriminate disposal. The ARVDs fall into this category, and although the risk assessment with respect to adverse effects and permissible level/threshold of nontarget exposure to these compounds have not been fully defined, there is growing scientific, public, and regulatory concern because these chemicals have been detected in surface water (Al-Rajab et al. 2010). The environmental hazard of a substance is described by its persistence, bioaccumulation in an organism's tissue, and toxicity. Therefore, before risk assessment of ARVDs can be carried out, there is a need for toxicological profiling based on these intrinsic properties (Escher et al. 2011; Deblonde and Hartemann 2013).

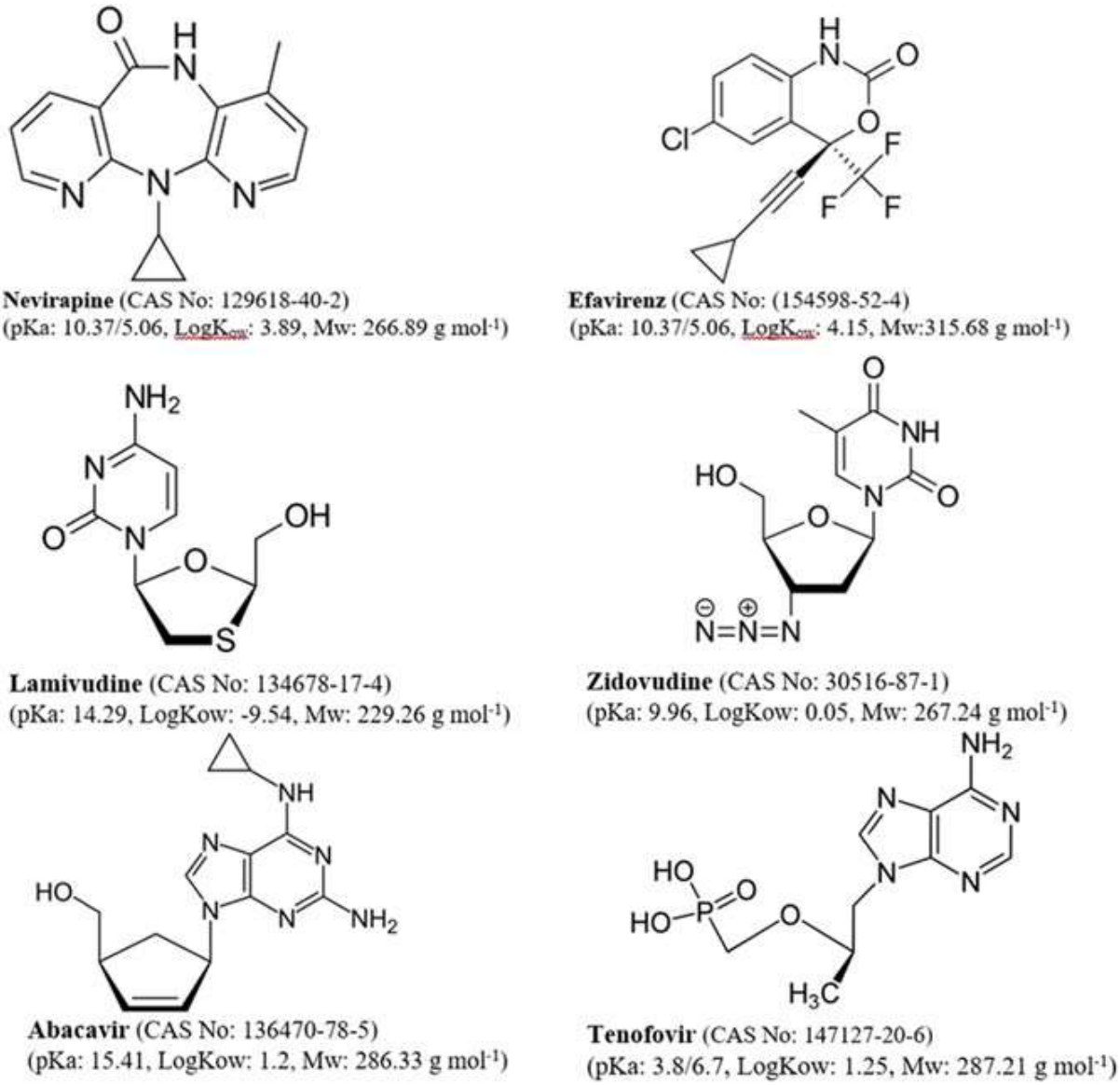

Figure 3. Structure of selected antiretroviral drugs with their physicochemical properties (from PubChem 2021). p*K*a = dissociation constant; log K_{OW} = octanol–water partition coefficient; Mw = molecular weight.

The overall aim of the present review was 1) to provide an African-based status report on the reported extent of ARVD–related water contamination, as a result of the increase in HIV infection and therapy on the African continent; 2) to explore the possible direct/indirect implications of such drug pollution on aquatic fauna and humans; and 3) to describe methods of analysis and a plausible adsorption mechanism of selected waterborne ARVDs onto carbon-based materials, as a possible remediation approach.

SOURCES AND FATE OF ARVD POLLUTION

The African continent is one the largest consumers of ARVDs, so it is rational to expect potentially higher environmental pollution by ARVDs as a result of poor waste management (Monteiro and Boxall 2010; Ferronato and Torretta 2019; Joint United Nations Programme on HIV/AIDS 2020). Sources of contamination by ARVDs include leaking septic tanks, underground sewage pipes, and runoff after rainfall on landfills (Wooding et al. 2017; Patel

et al. 2019). Improper domestic and sewage waste disposal, drug manufacture, hospital waste disposal, and agro-products containing metabolized and untransformed parent compounds are also important sources of ARVD contamination (Fick et al. 2009; Schoeman et al. 2015, 2017; Wood et al. 2016). Aside from ingestion of pharmaceuticals via prescription (or self-medication, which should be discouraged), human exposure to pharmaceuticals also occurs via the food chain, such as drinking contaminated water and eating food sources like crops, vegetables, fish, and dairy products (Ebele et al. 2017). The level of biotransformation that a drug compound undergoes in the body depends on its mechanism of action and physicochemical properties (Bound and Voulvoulis 2005). Some antiviral agents remain unchanged when consumed and are excreted as such (e.g., acyclovir), whereas others undergo extensive biotransformation before excretion from the body (e.g., lamivudine; Galasso et al. 2002; Razonable 2011).

The rate of consumption of ARVDs, based on epidemiological statistics for different countries in Africa, is uncertain, which means that it is difficult to ascertain the amount excreted into the environment. The number of people on ARVD treatment in Africa as of 2016 is presented in Figure 2. In South Africa, >20 tons of the drug combination of efavirenz, lamivudine, and disoproxil fumarate (brand name Symfi, for example) are consumed each day due to the widespread antiretroviral therapy program and HIV status awareness (Abers et al. 2014; Ncube et al. 2018). Other countries estimated to have consumed >1 ton of HIV antiretroviral medication/d are Kenya, Mozambique, Zimbabwe, Nigeria, and Uganda (Ncube et al. 2018).

The study by Ncube et al. (2018) indicates that >3.9 million people in South Africa are on antiretroviral therapy. Assuming that 3.9 million people are placed on antiretroviral therapy with a daily dose of a combination of ARVDs (mean of 991 mg/d/person, range 590–1996 mg/d/person), as reported by Schoeman et al. (2015), an average total of 1 411 554 kg of ARVD drug compounds are ingested per annum. Antiretroviral drugs such as tipranavir are excreted at 80% and nevirapine at 2.7% via urine; this value varies depending on the type of drug consumed (Schoeman et al. 2017). Assuming a mean of 30% of the drugs are excreted into sewage via urine and feces, then approximately 423 466 kg of ARVDs would reach the water bodies in South Africa each year. The excretion of ARVDs in urine and/or solid waste varies between 2.7 and 94% depending on the nature of the compound, but reports suggest that nevirapine and darunavir have the lowest and highest excretion percentages, respectively (Riska et al. 1999; Vermeir et al. 2009).

Other sources of ARVD contamination include leachate from landfills, effluents from hospitals, inadequate disposal of expired drugs, and waste dumped by research institutions and pharmaceutical companies. Disposal of out-of-date or unwanted medicines, which may occur via the sink/toilet or municipal landfill sites, means they may also eventually leach into groundwater. Prescription practices leading to some unfinished prescriptions contribute to the illicit disposal of unused drugs, thus compounding environmental pollution concerns regarding pharmaceutical products (Bound and Voulvoulis 2005; Orias and Perrodin 2013).

Amid very scarce information on the fate and ecotoxicity of ARVDs, there are reports that tenofovir (a type of ARVD) does not undergo microbial degradation in soils, because no

transformation products have been detected, suggesting that ARVDs could be very persistent and stable in soil (Al-Rajab et al. 2010). Another study (Aminot et al. 2018) indicated that hot climatic and aerobic conditions promote the partitioning of ritonavir into solid natural organic matter, resulting in between 5 and 40% adsorption by suspended solids in a river system. The same authors also reported that nevirapine and zidovudine are stable under wastewater treatment plant (WWTP) processes, whereas abacavir, lamivudine, ritonavir, and saquinavir had half-lives of <5 d under biochemical conditions for both wastewater and surface water samples tested (Aminot et al. 2018).

Laboratory-scale studies suggest that ARVDs undergo both photo- and biotransformation in water under environmental conditions, which means that longer holding times for effluents might provide cost-effective treatment solutions in developing countries (Prasse et al. 2010). Slightly >50% of zidovudine and nevirapine were eliminated from urine before application as fertilizer, during a hygienization process at 20 °C for 6 mo (Jaatinen et al. 2016). Chlorination disinfection of wastewater was reported to enhance the persistence of nevirapine and efavirenz due to the deconjugation of their hydroxylated metabolites, and reduction in binding ability of the compounds (K'Oreje et al. 2016; Wood et al. 2016). Unfortunately, none of these studies have been able to attribute the recalcitrance, stability, and persistence of ARVDs to their octanol–water partition coefficient (K_{OW}), logarithmic acid dissociation constant (p*K*a), and/or water solubility.

Although the environmental fate and impact of ARVDs on the environment have not been fully elucidated and understood, it has been established that unintentional and long-term intake of ARVDs from polluted potable water may lead to resistance to the drugs (Ncube et al. 2018; Mtolo et al. 2019). Therefore, there is an urgent need for a comprehensive environmental fate and impact assessment of ARVDs, and extensive monitoring of their concentrations in water bodies such as wastewater and surface water.

ARVD REMOVAL BY CONVENTIONAL WWTPs

Table 2 gives a summary of the levels of 2 major ARVDs in influents and effluents in WWTPs in African countries where studies have been carried out; these levels are compared with what has been reported in other parts of the world. Higher effluent treatment efficiencies were recorded with the advanced wastewater treatment methods adopted by Germany and Belgium, than with the conventional wastewater treatment procedures used in South Africa and Kenya. In addition, nevirapine and efavirenz were present at higher concentrations in influents studied in South Africa, requiring removal and suggesting the high rate of therapeutic application of these ARVDs (Abafe et al. 2018; Moslah et al. 2018). Table 2 also suggests that nevirapine is more recalcitrant to WWTP treatment methods than efavirenz when the influent–effluent ratios are considered. This can be attributed to the difference in physicochemical properties of the drug compounds.

TABLE 2: Levels of nevirapine and efavirenz reported in influents and effluents of wastewater treatment plants situated in some African countries compared with Europe

ARVD	Name of WWTP	Country	Concentration in influents (ng L^{-1})	Concentration in effluents (ng L^{-1})	Reference
Nevirapine	Jyväskylä	Finland	13–19	8–10	Ngumba et al. 2016a
	Cantinolle	France	—	<LOD–7.7	Aminot et al. 2015
	Ruhr	Germany	32	22	Prasse et al. 2010
	Decentralized	South Africa	2100	1900	Abafe et al. 2018
	Phoenix	South Africa	2800	1400	Abafe et al. 2018
	Northern	South Africa	670	540	Abafe et al. 2018
	Dandora	Kenya	850	1030	K'Oreje et al. 2016
	Nyalenda	Kenya	3300	2110	K'Oreje et al. 2016
	Kisat	Kenya	2080	2030	K'Oreje et al. 2016
Efavirenz	Gauteng	South Africa	17 400	7100	Schoeman 2015
	Decentralized	South Africa	34 000	34 000	Abafe et al. 2018
	Phoenix	South Africa	34 000	20 000	Abafe et al. 2018
	Northern	South Africa	24 000	33 000	Abafe et al. 2018
	Dandora	Kenya	780	110	K'Oreje et al. 2016
	Nyalenda	Kenya	460	100	K'Oreje et al. 2016
	Kisat	Kenya	1020	110	K'Oreje et al. 2016

WWTP = wastewater treatment plant; ARVD = antiretroviral drug; LOD = limit of detection.

The concentrations of efavirenz and nevirapine in treatment plants in eThekwini Municipality in KwaZulu-Natal, South Africa, ranged from 2100 to 34 000 ng L^{-1} (influent) and 1900 to 34 000 ng L^{-1} (effluent) in a decentralized wastewater treatment facility; from 670 to 24 000 ng L^{-1} (influent) and 540 to 33 000 ng L^{-1} (effluent) in Northern WWTP; and from 2800 to 34 000 ng L^{-1} (influent) and 1400 to 20 000 ng L^{-1} (effluent) in Phoenix WWTP (Abafe et al. 2018). The treatment plants recorded almost 90% removal efficiency for abacavir, lamivudine, and zidovudine from the effluents, but atazanavir, efavirenz, lopinavir, and nevirapine persisted in the effluents (Abafe et al. 2018, Madikizela et al. 2020); thus there is a need to study the ecotoxicological impact of the discharge of the persistent ARVDs into surface water.

Figure 4 shows a significant difference in the removal efficiency of WWTPs from one antiretroviral compound to another, even within the same treatment plant and under similar conditions (Mascolo et al. 2010; Prasse et al. 2010; Ngumba et al. 2016a, 2016b; Abafe et al. 2018). This can be attributed to the difference in physicochemical characteristics and behavior of the ARVDs, which makes them both recalcitrant and persistent to varying extents. Abafe et al. (2018) reported that conventional treatment plants in the study areas in South Africa and Kenya proved efficient for the removal of zidovudine, with a removal efficiency ≥99%, However, there are poorer results with the other types of ARVDs, which may lead to bioconcentration, bioaccumulation, and pollution of water bodies with adverse effects on living organisms.

Inefficient removal of ARVDs during the treatment of wastewater released from domestic and municipal sources is one of the major reasons why this class of organic micropollutants is detected in surface and drinking water. Treatment conditions play important roles in the efficiency of conventional WWTPs and membrane bioreactor treatment plants. Some of the factors affecting the optimum performance of treatment plants include sludge retention time, biomass/pollutant concentration, temperature, solution pH, and p*K*a of micropollutants, as well as membrane fouling (Cirja et al. 2008; Adeola and Forbes 2021a).

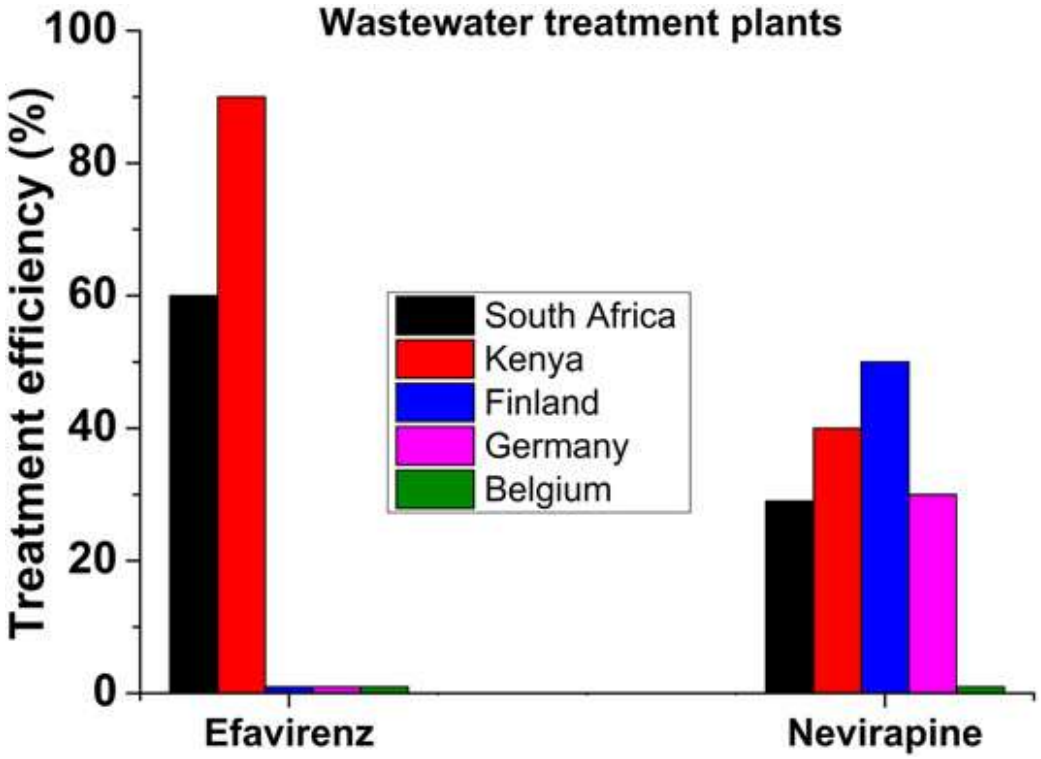

Figure 4. Antiretroviral drug removal efficiency of wastewater treatment plants (Mascolo et al. 2010; Prasse et al. 2010; Ngumba et al. 2016a, 2016b; Abafe et al. 2018).

DETECTION AND QUANTITATIVE ANALYSIS OF ARVDS

The indiscriminate discharge of ARVDs into the environment could have catastrophic effects on the biota of aquatic ecosystems (Mascolo et al. 2010). Some pharmaceuticals are nonbiodegradable and recalcitrant to environmental transformation processes (Daouk et al. 2015). Due to the possible bioaccumulation of metabolites or transformation products and parent compounds, the concentrations of these micropollutants in water bodies may increase over time. Thus, analytical methodologies have been developed for detecting and quantifying antiretroviral compounds at low levels in water bodies (in the ppb to ppt range; Mompelat et al. 2009).

Liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS) has been reported for the detection of 13 ARVDs (Abafe et al. 2018). That study was carried out on samples collected from 3 WWTPs in the eThekwini Municipality in KwaZulu-Natal. The method was validated, and the detection limits fell within a range of 2 to 20 ng L^{-1}. The recovery of ARVDs was >50%, with acceptable relative standard deviations. Lamivudine, a dideoxynucleoside reverse transcriptase inhibitor, potent for the treatment of HIV, was also analyzed by LC–MS, and the fragmentation pattern of the drug was elucidated by carrying out MS^n (up to MS^3) and MS/time-of-flight (TOF) studies in positive electrospray ionization (+ve ESI) mode (Bedse et al. 2009).

The 2-stage method involved concentration and clean-up by solid-phase extraction followed by identification and quantification by LC–ESI–MS/MS. The use of matrix-matched calibration curves constructed by spiking surface water was evaluated and compared with the internal standard method using isotopically labeled compounds (Ngumba et al. 2016b;

Mosekiemang et al. 2019). It was revealed that the use of stable isotopically labeled standards provided a more accurate quantification of ARVDs and offered an easy solution to ionization problems. The slope obtained from responses generated by the mass spectrometer, for the internal standard versus analyte concentration does not depend on matrix composition, thus eliminating the need for matrix-matching and yielding more accurate results (Hewavitharana 2011; Ngumba et al. 2016b).

Ultra-high-pressure liquid chromatography-tandem mass spectrometry (UHPLC–MS/MS) is a relatively new method that has been used in South Africa for the quantification of 12 antiretroviral compounds in surface water employing the standard addition method. Water samples were concentrated by a generic automated solid-phase extraction method and analyzed by UHPLC–MS/MS. The concentration of ARVDs reported ranged between 26.5 and 430 ng L^{-1} (Wood et al. 2015). Matrix interference/effects were a challenge during sample analysis, and an average limit of detection of 90.4 ng L^{-1} was reported.

A combination of comprehensive gas chromatography (GC×GC–TOFMS) and UHPLC–quadrupole (Q)TOF–MS/MS) for the determination of ARVDs by multiresidue analysis of surface water in South Africa has been reported (Schoeman et al. 2015; Wooding et al. 2017). An in-house developed polydimethylsiloxane sampler was used, and samples were analyzed with the aid of direct thermal desorption into the inlet of a GC×GC–TOFMS device. The large volume injection method was used during the UHPLC–MS/MS analysis for determination of ARVDs in surface water at ultratrace levels (Wooding et al. 2017).

A comparison between GC–TOFMS and quadrupole GC–MS using drug standards was carried out, which showed lower limits of detection (LODs) with GC–TOFMS similar to GC–electron capture detection. Furthermore, GC–TOFMS has the merits of high-quality full-scan mass spectra and high resolution (Aebi et al. 2002; Bergknut et al. 2006). A similar semiquantitative method was used for the determination of efavirenz and nevirapine in primary settling tank sludges from a WWTP using sonication extraction and GC–TOFMS analysis of samples collected in Gauteng, South Africa. Adequate method LODs and limits of quantitation (LOQs) of 3.9 and 12.9 mg kg^{-1}, respectively (for efavirenz). and 3.4 and 11.4 mg kg^{-1}, respectively (for nevirapine), were determined. The results were reproducible with high precision and accuracy. This affirms that the developed method can be adopted for the analysis of ARVDs, and it has proved to be efficient (Schoeman et al. 2017). However, the development of analytical methods that are easy, efficient, and ecofriendly continues to pose challenges, and more research and innovation are required (Forbes 2021).

Generally, the analysis of water for ARVDs involves sampling, transport, storage, preservation, sample preparation, analyte separation from matrix, detection, and quantification. There is a need for quality assurance because the target pollutants are present at trace levels, and therefore replicate analysis and spiking of samples should be performed as well as analysis of internal standards, surrogate standards, and certified reference materials. Most spectrophotometric methods have certain drawbacks such as low sensitivity, high limits of detection, and tedious experimental procedures. On the other hand, techniques based on LC–MS/MS and GC–TOFMS are relatively expensive while having advantages over other methods such as rapid analysis and a higher degree of resolution (Parastar et al. 2013). Thus, most researchers make them the first choice for precise and

accurate qualitative and quantitative analysis of pharmaceuticals. Furthermore, scarce resources, lack of equipment, and the high cost of maintenance of analytical instrumentation are major setbacks to the accurate detection and quantification of ARVDs in most countries in Africa.

CONCENTRATIONS OF ARVDS IN AFRICAN SURFACE WATER

The presence of ARVDs has been reported in surface waters (rivers and man-made lakes [dams]), as well as wastewater influents and effluents in Africa (Wood et al. 2015; Ngumba et al. 2016b, 2020; Abafe et al. 2018; Nibamureke et al. 2019). Surface waters around the globe have scarcely been studied for the presence of ARVDs; however, ARVDs have been detected in rivers and lakes in South Africa, Kenya, Zambia, and other parts of the world (Aminot et al. 2015; Funke et al. 2016; K'Oreje et al. 2016; Wooding et al. 2017, Mosekiemang et al. 2019; Madikizela et al. 2020; Ngumba et al. 2020).

The presence of ARVDs has been detected in surface water and wastewater in South Africa (Wooding et al. 2017), which is of concern because many rural dwellers and inhabitants of informal settlements in Africa collect untreated water from rivers and man-made lakes for personal use, due to limited access to treated water. A study was carried out that aimed to monitor the concentrations of nevirapine and efavirenz in the influent and effluent of a WWTP in Gauteng. Treated wastewater, before and after chlorination, was also examined to determine whether the target ARVDs were removed by chlorination (Schoeman et al. 2015; Wood et al. 2015). The concentrations of nevirapine and efavirenz in wastewater influent and surface water were found to be relatively high, within a range of 2100 to 17 400 ng L^{-1} and <LOD to 1480 ng L^{-1}, respectively, with a treatment efficiency of approximately 50%, which accounts for effluent concentrations of nevirapine and efavirenz within the range of 350 to 7 100 ng L^{-1}, respectively (Wood et al. 2015; Schoeman et al. 2017). These values are among the highest recorded in the literature for the analysis of water obtained from WWTPs, and chlorination did not improve the efficiency of the WWTPs beyond the 50% removal efficiency recorded without its inclusion.

The presence of ARVDs in various aqueous systems in Africa, such as raw WWTP effluents, surface water, groundwater, and even drinking water has been investigated (Ternes et al. 2002; Buchberger 2007; Kummerer 2008). Nevirapine (0.3–6.7 ng L^{-1}), efavirenz (0.3–3.5 ng L^{-1}), and didanosine (0.4–3.3 ng L^{-1}) have been detected in drinking water in South Africa (Swanepoel et al. 2015). The most prevalent ARVD detected in South African aquatic environments has been efavirenz with a concentration as high as 140 µg L^{-1} (Durban WWTP influent sample), whereas lower concentrations ranging from 0.002 to 2.45 µg L^{-1} have been detected in surface water samples (Rimayi et al. 2018; Mtolo et al. 2019; Ngqwala and Muchesa 2020).

A study was carried out to analyze water quality parameters and concentrations of 24 pharmaceutical compounds, which included antibiotic, antiretroviral, analgesic, anti-inflammatory, and psychiatric drugs in 3 WWTPs, 3 rivers, and 3 groundwater wells in Nairobi and Kisumu, Kenya. The spatial distribution of these emerging pollutants in water bodies was reported (K'Oreje et al. 2016; Ngumba et al. 2016a). Lamivudine (300–167 100 ng L^{-1}), zidovudine (40–17 410 ng L^{-1}), efavirenz (20–560 ng L^{-1}), and nevirapine

(330–5620 ng L^{-1}) were detected in 14 river samples collected in Nairobi and Kisumu. It was discovered that shallow wells with proximity to latrines contained the recalcitrant antiretroviral, nevirapine at concentrations as high as 1000 to 2000 ng L^{-1}, which may likely be due to underground seepage and groundwater movement; unfortunately, this untreated well serves as a drinking water source. Similarly, a high concentration range of nevirapine (1.1–228 µg L^{-1}) was detected in grab samples from a river in Machakos Town, Kenya, and ARVDs were more prevalent than antibiotics (Kairigo et al. 2020).

In Zambia, high concentrations of ARVDs were reported in surface water in the peri-urban area of Chunga in Lusaka (Ngumba et al. 2020). The ARVD concentrations ranged from <LOQ to 49 700 ng L^{-1} in surface water, and from 680 to 118,970 ng L^{-1} and 1720 to 55 760 ng L^{-1} in WWTP influent and effluent, respectively. The concentration of lamivudine (10 010 µg L^{-1}) in source-separated urine was higher than values recorded in wastewater in the Zambian study area. Similarly, nevirapine, ritonavir, emtricitabine, atazanavir, and darunavir were detected in the range of <1 to 920 µg L^{-1} in urine collection tanks at the University of KwaZulu-Natal (Bischel et al. 2015). Elevated concentrations detected in human urine suggest the need for precautionary measures in the application of urine as fertilizer. Furthermore, there is a need for treatment of urine before disposal, due to the high concentration of excreted ARVDs, to minimize potential environmental pollution (Udert et al. 2016).

The Orange River is the longest river in South Africa and the seventh longest river in Africa, stretching through South Africa, Botswana, Lesotho, and Namibia. The Orange River forms the southwestern boundary of the Free State Province of South Africa. It flows into the Gariep Dam (the largest in the country) and the Vanderkloof Dam (Figure 5). The Orange River meets with its main tributary, the Vaal River, and then flows further to the southern part of Northern Cape Province to meet with Namibia. The Orange River is highly susceptible to pollution by ARVDs, and varying concentrations of these toxic pharmaceuticals have been reported in the river (Madikizela et al. 2017). Several industrial, agricultural, and domestic activities are carried out along the river channels, which makes them vulnerable to pollution (Earle et al. 2005; Ramollo 2011; Wood et al. 2015). Figure 5 shows that the Gauteng Province is a major hotspot in South Africa, with most of the sampling and detection of ARVDs being found in and around Gauteng Province (Wood et al. 2015; Wooding et al. 2017), which may be attributed to the population density of the province.

A survey carried out by Wood et al. (2015) revealed that nevirapine, lopinavir, and zidovudine were frequently found throughout the selected rivers, man-made lakes, and WWTPs that were sampled. The drugs were present in the ppb (ng L^{-1}) range, with stavudine, nevirapine, and zidovudine having relatively higher concentrations. The Roodeplaat Dam system was included in the sampling because 2 WWTPs discharge effluents into the man-made lakes (the Zeekogat and Baviaanspoort WWTPs). Varying concentrations of pollutants were found in water samples of the 2 WWTPs. Samples from the Vaal River, the Orange River, and the confluence of these (taken within 100 m of each other), differed significantly (Figure 5), which highlights the need for comprehensive monitoring programs.

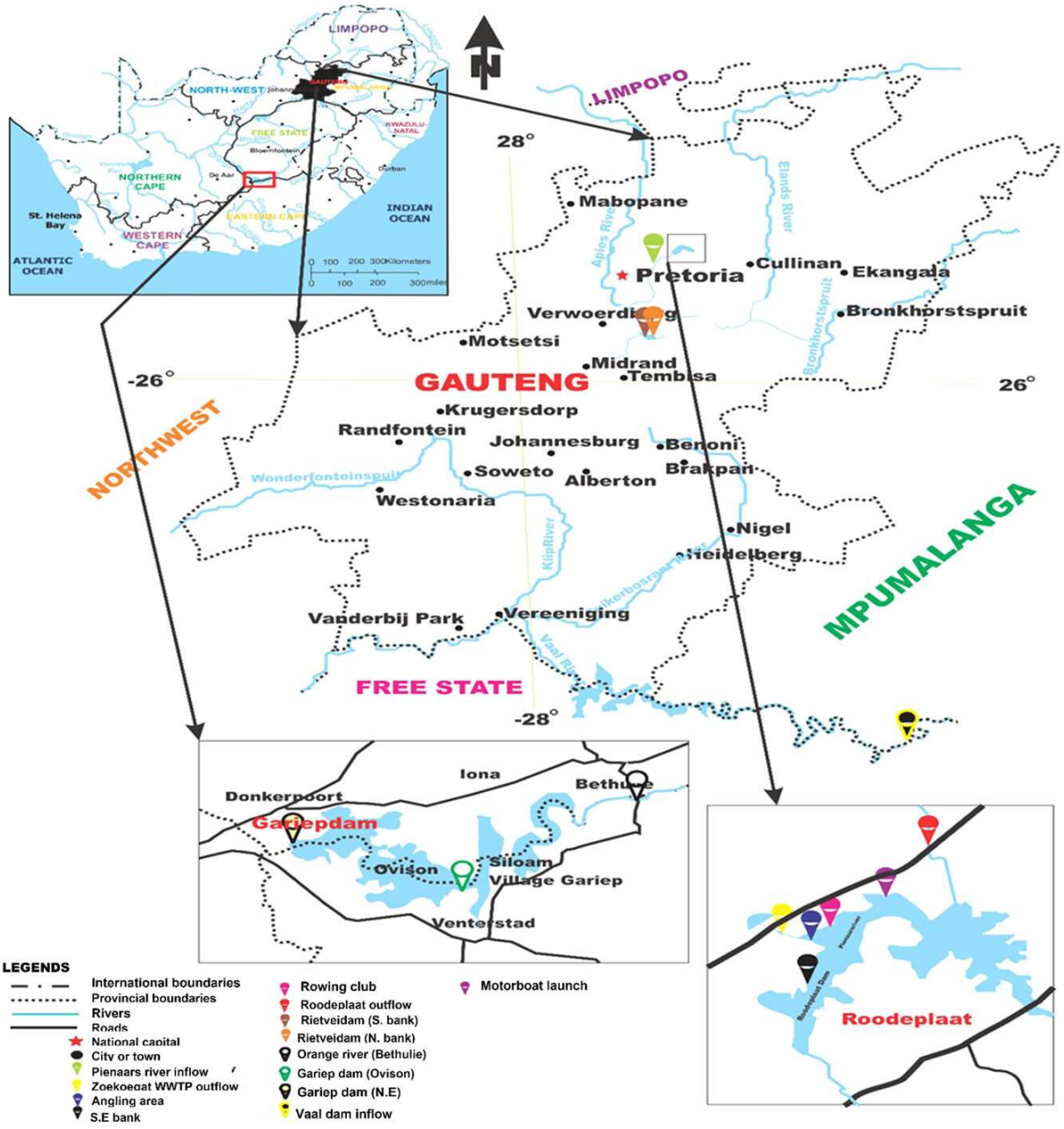

Figure 5. Location map of South Africa showing provinces and water bodies where antiretroviral drugs have been detected (Wood et al. 2015; Wooding et al. 2017). WWTP = wastewater treatment plant.

The Roodeplaat system study (Wood et al. 2015) revealed that ARVD concentrations were lower at the outflow point than at any other sampling point within the man-made lake. Points of higher concentration reported within the dam were possibly due to the depth and homogenization of the water in the area. The monitoring of this man-made lake was prioritized because it is used for recreation (fishing and water sport) and serves as a source of potable water (Wood et al. 2015). Nevirapine was above the LOD in all the surface water samples but could only be quantified at 9 of the 24 sampling locations. In influent samples collected in Kenya, the most frequently detected ARVDs were efavirenz, lamivudine, and nevirapine (K'Oreje et al. 2016; Mtolo et al. 2019, Kairigo et al. 2020), whereas efavirenz is typically most prominent in South Africa. There is vast variation in the concentration reported in the literature. However, whereas the highest concentration of efavirenz in

WWTP influents reported in Kenya was 12.4 μg L^{-1}, concentrations as high as 119 and 140 μg L^{-1} have been reported in Zambia and South Africa, respectively (Madikizela et al. 2020). The concentration of efavirenz detected in surface water is highest in Kenya (228 μg L^{-1}) and lower in South Africa (2.45 μg L^{-1}; Mtolo et al. 2019, Kairigo et al. 2020), possibly as a result of differences in waste management and WWTP efficiencies. The prevalence of this compound can be attributed to both its dominant therapeutic application and its persistence in the environment (Rimayi et al. 2018).

POTENTIAL EFFECTS ON HUMANS AND AQUATIC SPECIES

The therapeutic dose of efavirenz is 600 mg (once daily) and that of nevirapine is 200 mg (once daily for 14 d, followed by 200 mg twice daily) in adolescents and adults (Rosenbach et al. 2002). This regime was able to reduce the viral load to below the LOD after 48 wk, with 73% of 40 subjects displaying mild central nervous system effects, 33% diarrhea, and 10% rashes (Molina et al. 2000). The once-daily treatment regime for the management of HIV infection was adopted for convenience, improved adherence, and sustained virologic response. The potential for excretion of unmetabolized drugs into nontarget environments becomes worrisome given the daily dose and consistent usage for several weeks (Schoeman et al. 2015, 2017).

Antiretroviral drugs may cause adverse effects on the central and peripheral nervous systems (Abers et al. 2014). The rate and extent of neuropsychiatric adverse effects varies with different classes of ARVDs and among each drug in their class. Neurotoxicity induced by NRTI occurs due to the inhibition of mitochondrial DNA polymerase. This mechanism of action is also the reason for the mitochondrial myopathy and lactic acidosis that occurs with the use of zidovudine (Anderson and Rower 2010). Zidovudine and abacavir often cause central nervous system disturbances, such as mania and psychosis (Calmy et al. 2009). Efavirenz, which is an NNRTI, is predominantly associated with antiretroviral-related central nervous system toxicity, leading to insomnia, irritability, and vivid dreams (Abers et al. 2014). Three cases of renal toxicity (nephrotoxicity) have been reported in a study carried out in Paris, France (Legendre et al. 2003). The kidney problem was associated with the use of the antiretroviral agent tenofovir. Renal failure, proximal tubular dysfunction, and nephrogenic diabetes insipidus were diagnosed in one of the patients, and a diagnostic test called renal biopsy revealed chronic tubular necrosis with changes in the cells (nuclear changes) in the other 2 patients. Patients placed on tenofovir therapy should be closely monitored for symptoms of tubulopathy (glycosuria, acidosis, mild increase in plasma creatinine level, and proteinuria). A similar case of nephrotoxicity in a patient was reported with characteristic signs and symptoms of acute renal failure, Fanconi syndrome, and diabetes insipidus as a result of HIV-antiretroviral treatment using tenofovir (Verhelst et al. 2002).

Toxic epidermal necrolysis, or Lyell's syndrome, is a rare idiosyncratic life-threatening side effect of nevirapine administered to infants diagnosed with HIV infection (Tchetnya et al. 2018). Toxic epidermal necrolysis is characterized by severe cutaneous adverse reaction characterized by extensive detachment of the epidermis and mucous membranes, which could potentially lead to blindness in children (Thammakumpee and Yongsiri 2013). However, the World Health Organization recommends efavirenz and nevirapine as highly

active antiretroviral therapy (HAART) for low-income countries due to their low cost, efficacy, and easy accessibility (Tchetnya et al. 2018). Studies carried out in Cameroon, Malawi, and Thailand revealed that the earliest symptoms of toxic epidermal necrolysis developed after 8 d and potentially within the first 6 wk of the HAART regime using nevirapine (100 mg once daily for 2 wk and twice daily afterward for 2 wk, with cotrimoxazole antibiotics as prophylaxis against opportunistic infections; Manosuthi et al. 2006; Kiertiburanakul et al. 2009; Joseph et al. 2012). However, efavirenz has been reported to have a relatively lower risk (8–25%) of causing acute and chronic dermatological problems (Tchetnya et al. 2018).

Furthermore, nevirapine, a first-line ARVD, has been associated with chronic liver toxicity in humans after 200 mg was administered once daily for 14 d, followed by 200 mg twice daily (Gozalo et al. 2011). Adverse human health effects caused by ARVD exposures include cough, dizziness, fever, diarrhea, nausea, headache, rash, hepatotoxicity, hypersensitivity, psychosis, insomnia, fatigue, vivid dreams, idiosyncratic myalgia, dyslipidemia, pancreatitis, lactic acidosis, hepatic steatosis, and heart disease (Calmy et al. 2009; Hawkins 2010; Ncube et al. 2018). However, these adverse effects will only occur after exposure to elevated concentrations, drug abuse, overdose, and/or bioaccumulation of ARVDs over a long period and may not be relevant to exposure to low levels in the environment.

Degradation products of nevirapine cause skin rash and liver toxicity and there are growing concerns regarding exposure of nontarget aquatic organisms such as fish to highly specialized compounds such as ARVDs (Kolpin et al. 2002, Nibamureke et al. 2019). Research has shown that a concentration (1480 ng L^{-1}) of nevirapine detected in South African waters did not have significant detrimental effects on *Oreochromis mossambicus* (Mozambique tilapia fish) juvenile growth in terms of length and body mass initially, but a reduction in growth rate after 1 to 2 mo of exposure was observed (Nibamureke et al. 2019).

Antiviral drugs are believed to be one of the most hazardous therapeutic classes due to their toxicological profile with respect to daphnids, fish, and algae, with a maximum effective concentration (EC50) value of 57 mg L^{-1} but are regarded as less toxic to organisms such as crustaceans and diatoms, with EC50 values >100 mg L^{-1} (Sanderson et al. 2004; Minguez et al. 2016). Several antiviral drugs (efavirenz, nevirapine, etc.) and their metabolites (such as 8,14-dihydroxy efavirenz and 12-hydroxy-nevirapine) are nonbiodegradable, leading to their persistence in the environment (Accinelli et al. 2010; Mosekiemang et al. 2019; Madikizela et al. 2020). In this regard, there is a need for proactive advancement of existing sewage treatment plants and wastewater treatment facilities for optimal removal efficiencies.

Madikizela et al. (2017) have shown that current remediation or wastewater treatment methods only partially remove pharmaceutical pollutants from water, including ARVDs. Therefore, it is rational to expect that Africa, as the largest consumer of HIV ARVDs worldwide, would have more antiretroviral waste discharged into surface water. Careful consideration of the water cycle suggests that indiscriminate discharge of pollutants into water bodies or the environment inevitably puts humans at risk, either indirectly through the food chain, or directly through the drinking of untreated water. The lack of ARVD monitoring in drinking water, coupled with overdependence on untreated drinking water by

rural dwellers, increases vulnerability and health risks in Africa and other developing countries of the world (Ngumba et al. 2016a; Gwenzi and Chaukura 2018).

Adaramoye et al. (2012) published a study on the ecotoxicity of nevirapine (Viramune®) on specific organs of Wistar rats (liver, kidney, and testis). The rats were exposed to 18 and 36 mg kg^{-1} nevirapine according to body weight. There was no significant ($p > 0.05$) change in body weight or organs of interest for the 18 mg kg^{-1} exposure, nor were there clinical signs of toxicity. However, the higher dose (36 mg kg^{-1}) significantly ($p < 0.05$) increased the weight of the liver, serum total bilirubin level, and activities of γ-glutamyl transferase, alanine, and aspartate aminotransferases. A dose-dependent elevation of 107, 80, and 163% of malondialdehyde in the liver, kidney, and testis of the rats was recorded, respectively. This led to a decrease in hepatic, renal, and testicular functions. There was a 43% decrease in spermatozoa motility, 32% decline in sperm count, and 94% increase in sperm abnormalities. Histopathological findings revealed seminiferous tubule degeneration in the testis, severe liver necrosis, and elevated oxidative stress in rats exposed to elevated concentrations of nevirapine (Adaramoye et al. 2011).

In a study involving the administration of 1.2 mg of raltegravir and darunavir to adult mice, a mean concentration of approximately 15 000 ng mL^{-1} was found in liver serum and 27 000 ng g^{-1} in tissue after 1 h of administration, and the average concentration in the brain ranged from 150 to 200 ng g^{-1} of brain tissue. At 4 h post administration, the concentration was reduced to 300 ng mL^{-1} in serum and 1200 ng g^{-1} in tissue, with only traces in the brain (Asahchop et al. 2017). That study pointed out the role of exposure duration and variation in drug distribution in the biological host, as well as the fact that neuroinflammatory response was evident in brain tissues even at low concentrations. It will be informative to carry out ARVD toxicological studies on biota with due consideration given to human therapeutic dose and environmental concentrations, to establish a relevant correlation among dose-related response (median inhibitory concentration [IC50]/EC50), environmental exposure, and biological effects.

PROSPECTS AND POSSIBLE REMEDIATION TECHNOLOGIES

The remediation strategies developed over the years for pharmaceuticals, personal care products, and other organic contaminants in aqueous systems include chemical precipitation, ion exchange, membrane filtration, coagulation, photocatalytic degradation, and adsorption (Ahluwalia and Goyal 2007; Demirbas 2008; Fu and Wang 2011; Inyang et al. 2012; Zhang et al. 2014; Wang and Chen 2015; Uddin 2017; Wan et al. 2018).

Although it is acknowledged that mechanisms to prevent contamination of water sources are preferable to end-of-pipe treatment, poor sanitation and infrastructure may consequently lead to ARVD pollution of water. In this case, there are 4 approaches to water remediation: improve the efficiency of existing technology used in the operation of WWTPs, upgrade WWTPs with new remediation tools and technology, control the indiscriminate disposal of micropollutants, and isolate the source (Escher et al. 2011). The focus often includes end-of-pipe measures, such as effluent ozonation, or the application of activated carbon as an advanced tertiary treatment procedure. Ozonoation as a significantly efficient removal has been reported for pharmaceuticals (Hollender et al. 2009; Reungoat et al.

2010). The operational cost involved in the generation of radicals required for the oxidation process raises concerns, especially with the increase in the concentrations of target pollutants and large volumes of polluted water.

Photocatalytic degradation has been used for the breakdown of an ARVD (lamivudine) in water using titanium dioxide (TiO_2) as a catalyst (An et al. 2011). Three process variables, namely, TiO_2 dosage, pH, and lamivudine concentration, were selected to evaluate the efficiency of lamivudine degradation under varying conditions. The results obtained from modeling the surface response indicated that the extent of degradation of lamivudine was highly influenced by the TiO_2 dosage and initial concentration of the ARVDs. The optimum degradation efficiency was achieved at a suitable amount of TiO_2 catalyst and with a minimum concentration of lamivudine. Photocatalysis is an advanced oxidation technology that can be effective for antiretroviral decontamination of water and wastewater and should be explored. However, catalysts often possess limited reusability, due to the loss of catalytic activity with time, as a result of aggregation, fouling, deactivation, or side reactions, which are associated limitations (Sievers et al. 2016; Adeola and Forbes 2021a).

Irradiation by direct sunlight leading to direct and indirect photolysis has been reported for the degradation of ARVDs in water (Zhou et al. 2015). This further supports the fact that photodegradation is an important remediation process for many pollutants in surface waters. Three ARVDs (acyclovir, zidovudine, and lamivudine) were investigated in treated water, freshwater, and seawater under the irradiation from sunlight. The results obtained revealed that zidovudine was easily degraded via direct photolysis, whereas acyclovir and lamivudine were mainly transformed via indirect photolysis. The presence of certain chemical agents such as nitrates, bicarbonates, chloride ions, bromide ions, and dissolved organic matter, naturally occurring or induced, can also influence the rate and extent of transformation via photodegradation (Zhou et al. 2015).

Aerobic biodegradation proved to be efficient for the elimination of acyclovir in wastewater (Peng et al. 2014). Lamivudine can be subjected to forced decomposition by a hydrolytic method (under neutral, acidic, and alkaline conditions), oxidation, photolysis, and thermal stress. The drug is unstable in acid and alkaline conditions but remained stable under neutral pH. It was also degraded extensively in an oxidative environment into several possible degradation products that may be less harmful to the environment; however, this requires further study (Bedse et al. 2009). Another method that can be exploited for the removal of antiretrovirals is an integrated approach involving biodegradation and subsequent ozonolysis, which has proved to be an efficient method for the removal of transformation products of antivirals (carboxy-transformation products; Prasse et al. 2012; Knopp et al. 2016). The formation of carboxy-transformation products via oxidation of the hydroxyl moiety at the 5′ position results in loss of antiviral activity by decreasing the phosphorylation in infected cells. The hypothesis that induced loss of antiretroviral activity of ARVDs could potentially reduce hazards to humans and biota during nontarget exposure is subject to further research. Furthermore, whether there are stable forms of oxidized antiretrovirals is also unknown (Funke et al. 2016). Some antiviral compounds are nonbiodegradable, whereas others are degradable under certain environmental conditions, leading to potentially dangerous metabolites/degradation products. Thus, there is also a

need to develop analytical methods that delineate between parent compounds and transformation products with accuracy and precision.

Furthermore, nonpoint source/diffuse source contamination of surface water by ARVDs is among the major contributors to water pollution in Africa. Remedial protocols for surface water pollution can be carried out via in situ water treatment, as already described in this section, or via source control (Anawar and Chowdhury 2020). These methods are categorized into physical, chemical, biological, ecological, and engineering methods (Bai et al. 2020); however, for heavily polluted sites, single methods are often not effective, so the integration of 2 or more methods (integrated systems/hybrid techniques) is required (Adeola and Forbes 2021b). In the physical–engineering approach, aeration is an efficient and widely used technique for enhancing the growth and activity of microbes that could potentially degrade organic pollutants such as ARVDs that are present in wastewater, sewage, and landfills (Capodaglio and Olsson 2019). Similarly, ecological floating beds, wetlands, and biofilm reactors are techniques that adopt microorganism- and plant-based solutions for the remediation of organic chemicals from surface water or diffuse sources of pollution; these can be explored for effects against ARVD pollution (Anawar and Chowdhury 2020). Other engineering solutions include riverbank filtration, stormwater diversion, hydraulic structures, and dredging, all of which facilitate sedimentation, aeration, sunlight irradiation, and anoxic reactions, but they are very expensive.

A standardized hospital waste management system is vital to environmental safety with regard to the prevalence of ARVDs in surface water in Africa. The need for efficient sorting, collection, packaging, storage, and/or disposal of hospital and municipal waste cannot be overemphasized. Currently, negligence, ineffective collection, and transportation are responsible for poor hospital waste management in Africa (Faure and Rizzo Padoin 2003; Tsakona et al. 2007; Schoeman et al. 2017).

Adsorption of ARVDs using carbon-based adsorbents: A potentially viable water treatment method

The use of carbon-based adsorbents remains the most cost-effective method of remediation of pollutants in environmental matrices (Cao et al. 2009; Hua et al. 2012; Wang et al. 2015; Wan et al. 2015; Inyang et al. 2016; Adeola and Forbes 2021a). In practice, carbon-based adsorbents (including biochar derived from agricultural products/waste and carbonization of wood, graphene-based materials and carbon nanotubes, and granular activated carbon/powdered activated carbon) have been used in the adsorption of several environmental contaminants (Inyang et al. 2014; Ribeiro et al. 2015; Creamer and Gao 2016; Rajapaksha et al. 2016; Fang et al. 2017, 2018; Wang et al. 2017; Zhang et al. 2017; Zou et al. 2019; Adeola and Forbes 2020). Relative to other adsorbents, activated carbon represents a low-cost and environmentally friendly choice (Cai et al. 2019; Zhang et al. 2019). The enhanced adsorption affinity of graphene-based materials for several classes of emerging chemical pollutants has attracted scientific attention (Shen et al. 2015; Pérez-Ramírez et al. 2016; Xiao et al. 2016; Fraga et al. 2019; Adeola and Forbes 2021b), and holds promise for ARVDs.

Generally, organic pollutants such as efavirenz and nevirapine have low water solubility and are nonpolar, so hydrophobic interactions occur during adsorption onto hydrophobic surfaces of the carbon-based adsorbent. Rather than distributing within aqueous systems, ARVDs and other hydrophobic pollutants aggregate, thus creating surface tension and minimal contact with water in the process. Hence the selective adsorption of hydrophobic compounds in an aqueous medium by carbon-based adsorbents is enhanced by partitioning of sorbates and hydrophobic interactions with the sorbent (Adeola and Forbes 2020; Wang et al. 2020). The presence of benzene rings and other reactive functional groups such as –COOH, –OH, $–NH_2$, and so on. in carbon-based adsorbents and composites is important in their chemical modification (Yu et al. 2009, Yang et al. 2019). Possible mechanisms of interaction with ARVDs may include the formation of both covalent and noncovalent binding interactions, as well as hydrogen bonds between the –NH and –N group in nevirapine and efavirenz and carbon-based adsorbents. The aromatic rings of most carbonaceous adsorbents and composites, and the pyridinic/aromatic rings of ARVDs, may also provide a basis for possible hydrophobic interactions/bonding (Figure 6).

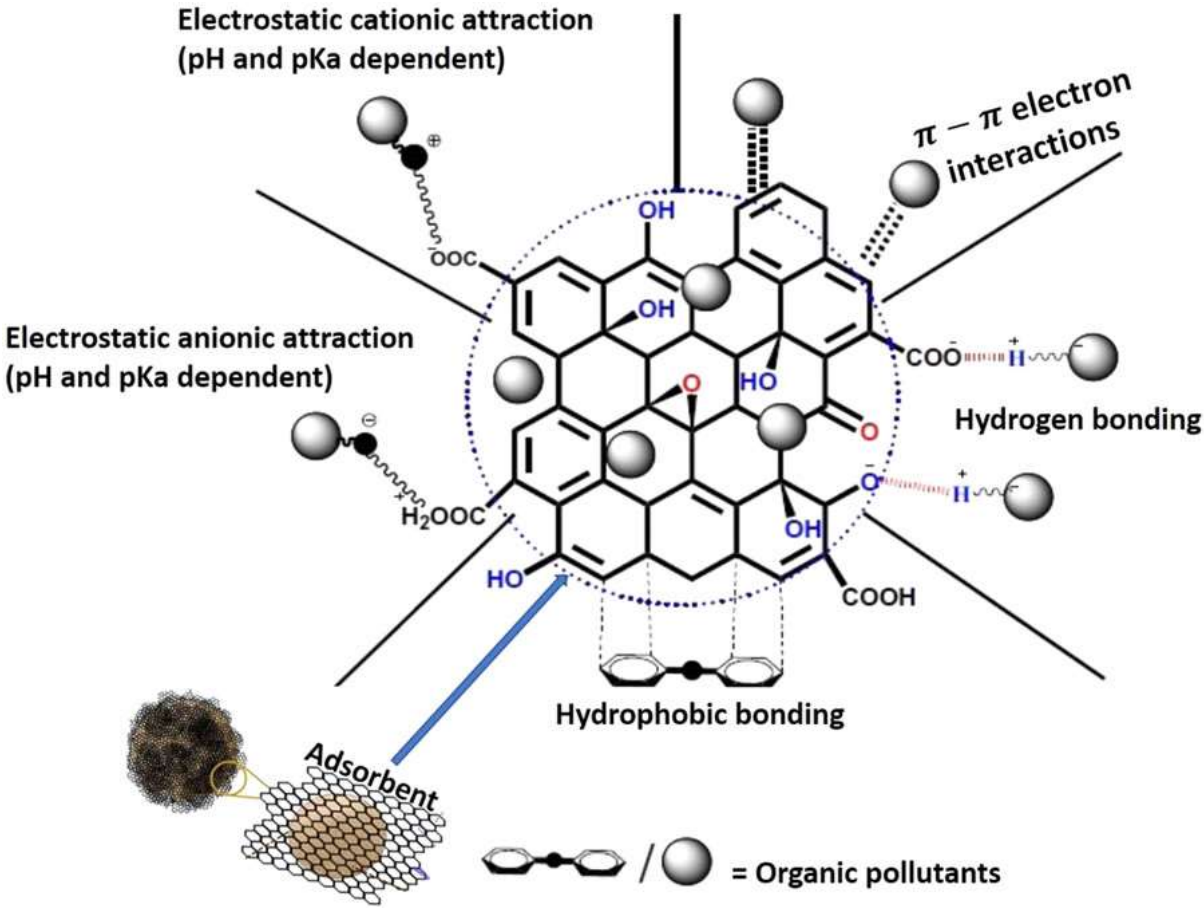

Figure 6. Different interactions between carbon-based adsorbents and organic pollutants. (Reproduced from Zhang et al. 2020 with permission from The Royal Society of Chemistry). p*K*a = dissociation constant.

Research on the adsorptive removal of ARVDs from surface waters and wastewater under variable environmental conditions (pH, temperature, and salinity) and the role of natural organic matter has not been reported to date. Hence there is an urgent need to investigate the optimum conditions for the removal of antivirals/ARVDs from wastewater and surface water.

CONCLUSIONS AND RECOMMENDATIONS

The release of ARVDs into the aquatic environment via wastewater, if they are not biodegraded or removed in WWTPs, may lead to environmental pollution and hazards resulting from bioaccumulation and nontarget exposures. Several publications have reported that ARVDs are present in wastewater, rivers, lakes, and in some cases drinking water in Africa. It is important to determine the total bioavailable ARVD compounds in surface water and effluents because this indicates the amount of the compounds that can potentially be taken up by biota in water. Future research should concentrate on the risk assessment of ARVD hotspots; the fate, environmental behavior, and ecotoxicology of ARVDs; and cost-effective interventions to minimize the associated health risks.

Furthermore, we recommend the following considerations going forward.

Pollution potential

Healthcare workers and drug manufacturers need to consider the pollution potential of industrial waste, overprescription, and hospital wastes.

Dose-related responses

Data/information are scarce in terms of relevant ecotoxicological endpoints with respect to human and biota lethal dose/exposure; therefore future studies should consider both the human therapeutic dose and the environmental concentrations, to establish a relevant correlation among dose-related response (IC50/EC50), total bioavailable fraction, environmental exposure, and biological effects.

Setting permissible levels

Africa currently does not have extensive environmental monitoring programs and legislative guidelines for ARVD-related waste management, which implies that there are no maximum permissible levels for the antiretroviral class of compounds in various environmental compartments. Therefore, there is a need for a synergistic effort between international and regional regulatory bodies, in conjunction with experts, to carry out a comprehensive risk assessment of ARVDs in water bodies and to set a permissible level for ARVD concentrations in effluents discharged into water bodies.

Better water treatment methods

There is a need for the development of better and more efficient wastewater, sewage, and drinking water treatment methods in Africa, to minimize the risk of exposure and its consequences. More compact, cost-effective, versatile, and efficient treatment methods such as membrane technology, adsorption, and integrated systems should be given closer attention because they have the advantage of purifying wastewater, without the extensive use of chemicals.

Upgrading of WWTPs

Due to the increasing demand for clean and safe water, there is an urgent need to ensure reusability; thus WWTPs should be well maintained and upgraded to handle the fast-growing environmental and economic demands for clean and safe water, as described by the United Nations Sustainable Development Goals (United Nations 2015).

Research collaboration and adequate funding

In conclusion, the lack of advanced analytical facilities in most African countries and other developing regions of the world will continue to constrain research and monitoring efforts. Therefore, there is a need for public–private partnerships among government agencies, healthcare providers, and pharmaceutical companies, in areas of research funding and development, to ensure that the prevalence of emerging pollutants in water bodies does not destroy our ecosystems.

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Author Contributions Statement

A. Adeola: conceptualization, investigation, formal analysis, and writing of original draft; and P. Forbes: formal analysis, writing review and editing, fund acquisition, and supervision.

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