

Original Research

Environmental Risk Assessment of Antiretrovirals Consumed in Belo Horizonte, BrazilMíriam de Fátima Soares ¹, Frederico Keizo Odan ¹, Marcos Paulo Gomes Mol ^{2,*}

1. Centro Federal de Educação Tecnológica de Minas Gerais - CEFET-MG, Belo Horizonte, Brazil; E-Mails: mfsquimica2@gmail.com; frederico_keizo@yahoo.com.br
2. Fundação Ezequiel Dias (Funed), Belo Horizonte, Brazil; E-Mail: marcos_mol@yahoo.com.br

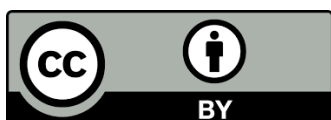
* **Correspondence:** Marcos Paulo Gomes Mol; E-Mail: marcos_mol@yahoo.com.br**Academic Editor:** Chow Ming Fai**Special Issue:** [Advances in Healthcare Waste Management](#)*Adv Environ Eng Res*

2025, volume 6, issue 4

doi:10.21926/aeer.2504034

Received: June 09, 2025**Accepted:** November 24, 2025**Published:** December 04, 2025**Abstract**

The development and utilization of pharmaceuticals, notably antiretrovirals (ARVs), have significantly enhanced both human quality of life and life expectancy. Nevertheless, the excretion of these compounds into aquatic environments, often exacerbated by inadequate sanitation infrastructure, poses considerable risks to biota. This investigation evaluated the environmental impact of 14 ARVs consumed within the municipality of Belo Horizonte (BH), Brazil. The assessment employed the Environmental Risk Assessment (ERA) framework, incorporating future scenarios projected to 2050 via Monte Carlo Simulation (MCS), and utilized Sensitivity Analysis (SA) to identify the most influential variables within the ERA model. All investigated ARVs exhibited predicted environmental concentrations (PECs) exceeding 10 ng/L, except for the results from the adapted 2006 model. According to both the 2006 and 2018 models, lopinavir, maraviroc, and ritonavir warranted progression to a Phase II-Level B analysis. This indicated a potential environmental risk in the 2006 model, whereas the 2018 model suggested no such risk. In the MCS projections for 2050, all standardized ARVs indicated risk in 100% of the baseline simulation events, yielding Risk Quotients (RQ) greater than 1 for all compounds. The SA revealed that the standardized model is more sensitive to the



© 2025 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

population variable, whereas the 2006-adapted model is predominantly influenced by the excretion factor. This study underscores the imperative of assessing the environmental impact of ARVs. It highlights the necessity for implementing mitigation measures - such as enhancements in wastewater treatment and sanitation systems - to curtail the adverse effects propagated by these pharmaceuticals.

Keywords

Environmental risk assessment; monte Carlo simulation; sensitivity analysis; ecotoxicity; antiretrovirals; Brazil

1. Introduction

The municipality of Belo Horizonte (BH), situated in the state of Minas Gerais, Brazil, possesses a sanitary sewerage network coverage of 93.9%, a figure that substantially exceeds the national average of 68.3% [1-3]. The Sanitation Company of Minas Gerais, COPASA, administers sanitation services within the municipality. Nonetheless, approximately 6.1% of residences still lack access to the sanitary sewerage system, and 12.04% of wastewater collected in BH is discharged without treatment [4].

Compounding this situation, extant scientific literature demonstrates that conventional wastewater treatment processes are insufficient for the complete removal of all contaminants [5-10]. Consequently, pharmaceutical compounds such as antiretrovirals (ARVs) - classified as pseudo-persistent pollutants by Abafe et al. [11] and as environmental organic micropollutants by Adedapo et al. [9] - may elicit deleterious effects in biota upon entering surface waters. These effects include disruptions to reproductive and endocrine systems, neurobehavioral alterations, and the development of pathogen resistance [9]. Furthermore, human ingestion of these substances via potable water supplies is a documented risk, potentially inducing resistance to retroviruses, notably the Human Immunodeficiency Virus (HIV), particularly in infected individuals [8].

The literature consistently indicates that pharmaceuticals, many of which are characterized as ecotoxic or recalcitrant, are not wholly eliminated during conventional multi-stage sewage treatment. Treated effluent, therefore, constitutes a significant pathway for the introduction of these compounds into receiving surface waters [12].

Consequently, the application of models capable of predicting ARV concentrations in aquatic environments is imperative. In this context, the Environmental Risk Assessment (ERA) framework proposed by the European Medicines Agency (EMA) [13, 14] is particularly prominent.

It is likewise crucial to analyze the potential for these substances to pose environmental risks in future scenarios, either exacerbating current risks or their continuation. To this end, predictive modeling can be employed, often integrated with Monte Carlo Simulation (MCS) techniques to stochastically evaluate potential outcomes based on the study variables. Such models can be coupled with Sensitivity Analysis (SA), which permits the identification of variables that exert the most significant influence on the escalation of environmental risk.

Accordingly, the present study aims to evaluate the ecotoxicity of ARVs consumed in Belo Horizonte, Brazil, utilizing the ERA model. It further seeks to analyze future scenarios regarding the

potential risk these pharmaceuticals pose to the aquatic environments of Belo Horizonte. A secondary objective is to propose an adapted ERA model, detailing procedures for its contextual adaptation, while concurrently identifying potential future contamination profiles to report on proposed preventive and mitigating measures to control pollution.

The selection of Belo Horizonte as the locus of this investigation is justified by its strategic geographic location, as the municipality is situated within the hydrographic basin of the São Francisco River, one of Brazil's most vital river systems, which ultimately discharges into the Atlantic Ocean. Moreover, a review of recent literature revealed a paucity of studies on this subject, thereby highlighting the novelty and significance of this research for both the scientific community and society at large.

2. Methods

2.1 Data Acquisition

Data on ARVs consumption in Belo Horizonte were procured from the official registries of the Testing and Counseling Center/Specialized Assistance Service (CTA/SAE) Sagrada Família, encompassing the period from 2018 to 2020.

2.2 Environmental Risk Assessment (ERA)

Within the ERA framework, utilizing both the 2006 and 2018 guidelines, the process commenced with the calculation of the Predicted Environmental Concentration for surface water (PEC_{SW}) during Phase I. Subsequently, in Phase II - Level A, the Risk Quotient (RQ) was determined for pharmaceuticals that exhibited a Phase I PEC_{SW} exceeding 10 ng/L or possessed an octanol-water partition coefficient (K_{ow}) value greater than 4.5.

Should the RQ exceed 1, Phase II - Level B was initiated. This phase entails the calculation of a refined PEC_{SW} by meticulously scrutinizing the environmental pathways of the pharmaceutical. This calculation accounts explicitly for the human excretion rate, the residual fraction remaining after wastewater treatment, the specific market penetration factor of the drug within the analyzed population, and the quantity of the drug adsorbed to suspended solids. The equations (1-7) employed in these circumstances are detailed below, with the utilized variables presented in Table 1.

Table 1 Variables used in the 2006 and 2018 ERA model.

Variable	Explanation
PEC _{SW,I}	Initial predicted environmental concentration in surface waters (mg/L).
DOSE	Consumed daily dose of the active compound (mg/inhab.d): This metric represents the per capita daily consumption of the studied active pharmaceutical ingredient. For the standardized calculation, this value was derived from the dosage information specified in the prescribing information (or summary of product characteristics) for each medicinal product. The highest maximum recommended daily dose stipulated for any patient subgroup was adopted, thereby modeling a worst-case

	scenario. Conversely, for the BH-specific values, consumption data were procured from the CTA/SAE Sagrada Família. This aggregate figure was subsequently normalized by dividing it by the number of days in a month (standardized as 30) and further by the total population of Belo Horizonte for the year 2020, as reported by the IBGE [15]. This variable corresponds to the $DOSE_{AS}$ parameter as defined in the EMEA guidelines [14].
$F_{pen.STD}$	Standard Penetration Factor, which represents the fraction (%) of the population undergoing treatment with a specific drug substance, was assigned the adopted value of 1% in accordance with the governing directives. This parameter was omitted from the non-standardized calculation.
$WASTE_{W.inhab}$	Daily amount of sewage generated per inhabitant (L/inhab.day): For the standardized calculation, a value of 200 L/inhab.day was adopted, consistent with the governing directives. Conversely, for the BH-specific parameters, the per capita daily water consumption figure (utilizing 2017 data sourced from the IBGE [15]) was employed. This value was subsequently multiplied by the wastewater return coefficient of 0.8, which is the factor adopted for the state capital (Belo Horizonte) as stipulated by Technical Standard T 234/1.
DILUTION	Sewage dilution factor in wastewater (dimensionless): A standard value of 10 was adopted for this parameter, in accordance with the EMEA guidelines.
PNEC	Predicted No-Effect Concentration (g/L): The value was established utilizing Daphnia species, selected to represent the most sensitive organism. Consequently, drawing from data presented by Marzabal et al. [16], an Assessment Factor (AF) of 10 was applied to the No Observed Effect Concentration (NOEC). This factor corrects the extrapolation for chronic exposure in freshwater environments [7], yielding the Predicted No-Effect Concentration (PNEC) via the equation: $PNEC = NOEC/10$.
$PEC_{sw.II}$	Refined predicted environmental concentration for surface water (mg/L): This parameter was calculated utilizing both EMEA standardized data [13, 14] and data specific to BH, designated as $PEC_{SW.II.EMEA}$ and $PEC_{SW.II.AC}$, respectively.
$E_{local.water}$	Local emission to wastewater of the relevant residue (mg/d).
$F_{stp.water}$	Fraction of the substance that remains in the effluent from a sewage treatment plant after treatment (STP) (%): this value was derived from Abafe et al. [11] and represents a weighted average of the figures reported therein. Its adoption was premised on the methodological similarities observed between the treatment processes at the STPs in Belo Horizonte and those documented in the cited study.
$WASTE_{collected}$	Percentage of collected sewage (%): For the $PEC_{SW.II.EMEA}$ calculation, a

	value of 1 was presumably adopted, whereas for $PEC_{SW.II.AC}$, the figure of 0.939, sourced from Trata Brasil [3] and corresponding to the year 2019, was employed.
FACTOR	Fraction of the active compound absorbed by the matter in suspension (%): For the calculation of $PEC_{SW.II.EMEA}$, a value of 0.1 was adopted. In contrast, the $PEC_{SW.II.AC}$ calculation utilized the organic compound-soil sorption coefficient ($K_{OC.soil}$), which was procured from the PubChem database [17, 18]. According to the EMEA [14] framework, this parameter is determined via equation 13.
F_{pen}	The Specific Penetration Factor represents the fraction (expressed as a percentage) of the population undergoing therapeutic treatment with a given active substance.
$C_{localEFF}$	Concentration of an active substance in the STP effluent (mg/L).

It is pertinent to note that the 2006 ERA model was simulated utilizing both default (standard) parameters and site-specific parameters for BH. This dual approach facilitated a comparison between the values stipulated by the European agency and the results derived from the adapted model. Conversely, the 2018 ERA model was simulated exclusively using default parameters. Further details regarding the employed equations are available in the Supplementary Information.

2.2.1 ERA - 2006

PHASE I.

$$PEC_{SW.I.EMEA} = \frac{DOSE_{EMEA} * F_{pen STD}}{WASTE_{inhab.EMEA} * DILUTION} \quad (1)$$

PHASE II - LEVEL A.

$$RQ = \frac{PEC}{PNEC} \quad (2)$$

PHASE II - LEVEL B.

$$PEC_{SW.II} = \frac{E_{localwater} * F_{stp water} * WASTE_{collected}}{WASTE_{inhab} * CAPACITY_{stp} * FACTOR * DILUTION} \quad (3)$$

2.2.2 ERA - 2018

PHASE I.

$$PEC_{SW} = \frac{DOSE_{AS} * F_{pen}}{WASTE_{inhab} * DILUTION} \quad (4)$$

PHASE II - LEVEL A.

$$RQ = \frac{PEC}{PNEC} \quad (5)$$

PHASE II - LEVEL B.

$$PEC_{SW-REFINED} = \frac{C_{local_{EFF}}}{DILUTION * FACTOR} \quad (6)$$

$$RQ_{SW-REFINED} = \frac{PEC_{SW-REFINED}}{PNEC_{SW}} \quad (7)$$

Population Projection.

The logistic population projection equation (Eq. 8) was calibrated utilizing official census data for Belo Horizonte, for the years 1900, 1920, 1940, 1950, 1960, 1970, 1980, 1991, 2000, and 2010. These computations were performed in a Microsoft Excel 2019 spreadsheet environment, specifically using the Solver add-in.

$$P_t = \frac{P_s}{1 + c * e^{K_1(t-t_0)}} \quad (8)$$

The equation was calibrated by adjusting the parameters P_s , c , and K_1 to optimize the fit of the logistic model against the observed population data, specifically the historical censuses of BH. Consequently, to minimize the deviation between the modeled projection and the empirical population figures, the Mean Absolute Error (MAE) was minimized, as detailed in Eq. 9. The variables employed in the population projection equations are presented in Table 2.

$$MAE = |P_{obs} - P_{est}| \quad (9)$$

Table 2 Variables used in population projection equations.

Variable	Explanation
P_t	Projected population for year t (inhab)
P_s	Saturation population (inhab)
c	Constant
K_1	Logistical constant
t	Projection year
t_0	Year of the first demographic census considered
MAE	Mean Absolute Error (inhab)
P_{obs}	Observed population (inhab)
P_{est}	Estimated population (inhab)

Ultimately, two distinct population projection scenarios were formulated for Belo Horizonte, based on the United Nations (UN) [19], concerning the Brazilian population and incorporating a 95% confidence interval. The population projection derived from Equation 8 was calibrated as equivalent to the UN median forecast (2016). Subsequently, using proportional calculation, minimum and maximum values were derived to align with the 95% confidence interval. These were designated as the “low projection” and “high projection” scenarios, respectively.

Monte Carlo Simulation (MCS).

Within the Monte Carlo Simulation (MCS) framework, the input variables were assumed to adhere to a uniform distribution. The stochastic variables subjected to randomization included: Population, $WASTE_{inhab.AC}$, $F_{stp.water}$ and feces. For these variables, random values were generated within their respective pre-defined minimum and maximum bounds. The simulation was calculated using the generic equation (Eq. 10). This MCS methodology was applied to both the 2006 and 2018 ERA models. The variables employed in the generic MCS equation are presented in Table 3.

$$V_{rand.} = V_{min.} + \left[(V_{max.} - V_{min.}) * f(ALEATÓRIO()) \right] \quad (10)$$

Table 3 Variables used in the generic MCS equation.

Variable	Explanation
$V_{rand.}$	Variable with a generated random value
$V_{min.}$	Minimum value that each variable can reach
$V_{max.}$	The maximum value that each variable can reach
$f(ALEATÓRIO())$	Function of Microsoft Excel 2019 Spreadsheet Editor Library

The uniform distribution is selected over a normal or log-normal, not to model data directly, but as a fundamental computational tool. It serves as a source of random cumulative probabilities for inverse transform sampling. By feeding these uniform values into the inverse function of any target distribution (like normal or log-normal), it generates correctly distributed samples. Thus, uniformity is chosen for its mathematical versatility in generating other distributions, not for its shape.

To determine the sufficient number of events, each event constituting a unique combination of randomized variable values, the model's convergence was evaluated. This assessment focused on the Population and $WASTE_{inhab.AC}$ variables. To this end, the mean and standard deviation were computed for 10 distinct scenarios, utilizing event counts of 100, 1,000, 10,000, and 20,000.

It is pertinent to note that the $WASTE_{collected}$ variable was projected to the year 2050 utilizing a linear regression model, which was predicated on data sourced from Trata Brasil [3].

Sensitivity Analysis (SA).

Finally, a Sensitivity Analysis (SA) was performed for Phase II - Level B of the ERA model 13 - summarized by equation 11, 12, and 13, encompassing only those ARVs for which complete data were available for both the standardized and BH-specific calculations. This analysis aimed to determine which factors exert the most significant influence on the system under study. The sensitivity computation involves the Sensitivity Index (SI) and the Stability Index (EI). The mathematical formulations for these indices are presented below, and their calculations were conducted in accordance with the ceteris paribus principle. The analysis generated the equations given below, with the corresponding variables detailed in Table 4.

$$PEC_{SW.II} = \frac{\left[DOSE * F_{excreta} \left(\frac{CONSUMPTION * 100}{DDD * inhabitants * 365} \right) * CAPACITY \right] * F_{stp.water} * WASTE_{collected}}{WASTE_{inhab.} * CAPACITY * FACTOR * DILLUTION} \quad (11)$$

$$SI_{VF} = \frac{[F(V_0 + \Delta V) - F(V_0 - \Delta V)]}{2 * \Delta V} \quad (12)$$

$$EI_{VF} = \left[\frac{V_0}{F(V_0)} \right] * SI_{VF}$$

(13)

Table 4 Variables used in the SI and EI equations.

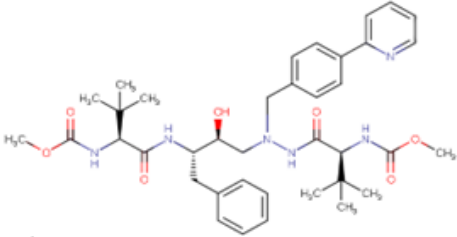
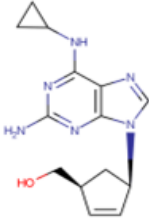
Variable	Explanation
F	Output variable or function
V	Parameter or input variable
ΔV	Variation of V in relation to a base value V ₀
SI _{VF}	F sensitivity index in relation to V
EI _{VF}	Elasticity index of F in relation to V

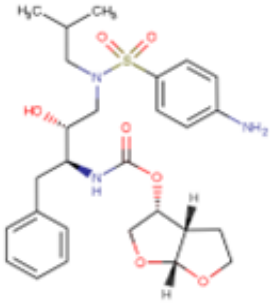
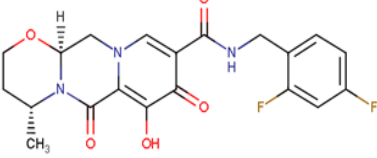
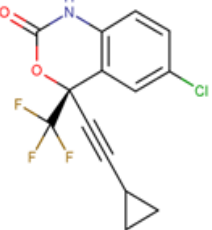
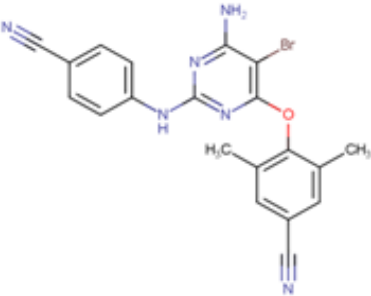
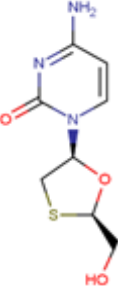
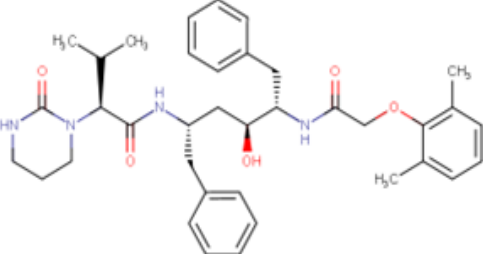
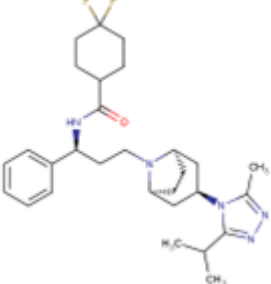
3. Results

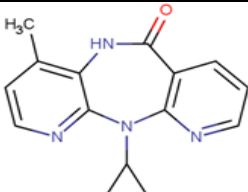
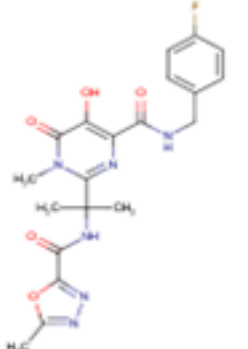
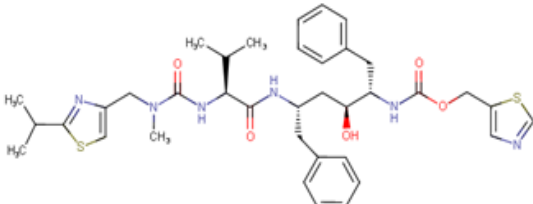
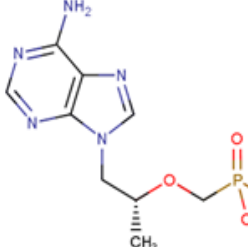
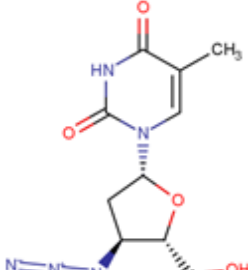
3.1 Preliminary Data

This investigation encompassed all ARV pharmaceuticals consumed within the municipality of Belo Horizonte during the period spanning 2018 to 2020. In total, 14 ARVs were enumerated for analysis: atazanavir (ATZ), abacavir (ABC), darunavir (DRV), dolutegravir (DTG), efavirenz (EFZ), etravirine (ETR), lamivudine (3TC), lopinavir (LPV), maraviroc (MVQ), nevirapine (NVP), raltegravir (RAL), ritonavir (RTV), tenofovir (TDF), and zidovudine (AZT). The pertinent physicochemical characteristics of these compounds are detailed in Table 5, where the substances are designated by their respective acronyms.

Table 5 Table with the main physicochemical properties of the studied ARVs*. Source: Drugbank [18]; Pubchem [17].

ARV	E. Lewis	K _{oc}	Log K _{ow}
ATV		3.8·10 ⁷	2.88
ABC		-	1.2

DRV		-	1.88
DTG		-	1.62
EFZ		-	4.7
ETR		$1.7 \cdot 10^4$	5.54
3TC		-	-9.54
LPV		$1 \cdot 10^6$	5.94
MVQ		-	5.80

NVP		-	3.89
RAL		95	0.40
RTV		-	6.27
TDF		-	-1.6
AZT		-	0.05

*E. Lewis is the Lewis structure, K_{OC} is the organic carbon adsorption coefficient, and $\text{Log } K_{OW}$ is the decimal logarithm of the octanol/water partition coefficient. Consider the character “-” as missing data.

Figure 1 illustrates the consumption data for the 14 aforementioned ARVs spanning the 2018 - 2020 period. These data, originating from the SAE Sagrada Família, were subsequently extrapolated to represent the entire BH population. The analysis highlights 3TC (lamivudine) and TDF (tenofovir) as the most substantially consumed agents, with monthly consumption of 25.7 kg and 22.7 kg. This elevated usage is attributed to their inclusion in fixed-dose combination regimens, such as tenofovir + lamivudine + efavirenz, tenofovir + lamivudine, and zidovudine + lamivudine [20]. Conversely, lopinavir had the lowest consumption at 60 mg/month, whereas this medicine is typically available in a co-formulation with ritonavir [21].

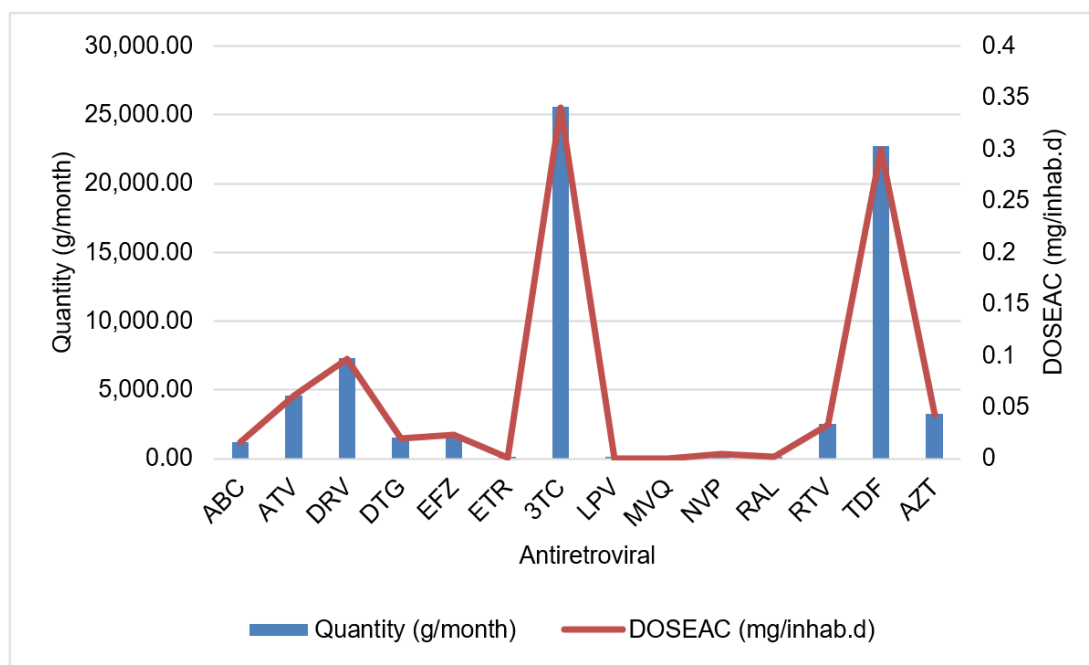


Figure 1 Data pertaining to antiretroviral consumption spanning the 2018-2020 period (monthly average). Source: Authors.

3.2 ERA Model (2006)

Figure 2 presents the consolidated results from all phases of the ERA model [13], contrasting standardized parameters against adapted parameters. In Phase I, it was observed that when standardized values were used, all pharmaceuticals exhibited PECs exceeding 10 ng/L.

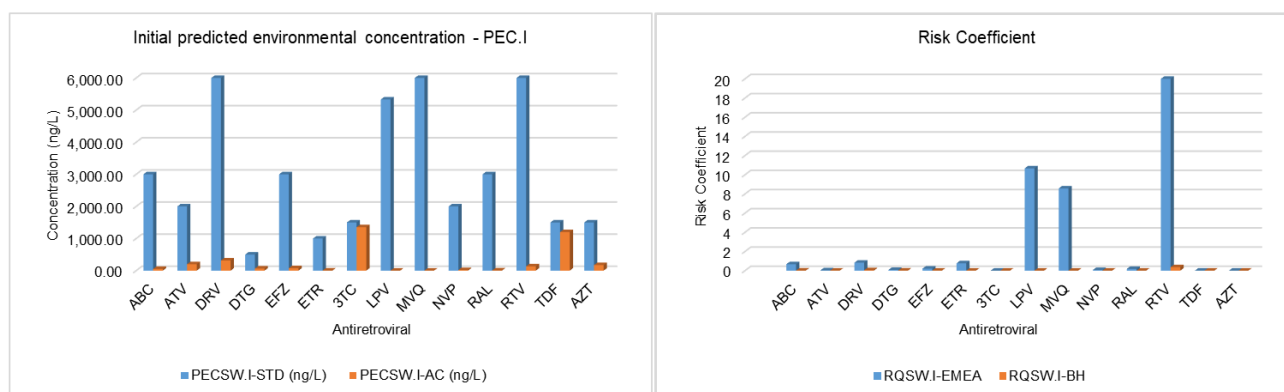


Figure 2 Results of applying the ERA model [13]. Source: Authors.

Conversely, when employing the adapted (BH-specific) values, etravirine, lopinavir, maraviroc, nevirapine, and raltegravir yielded concentrations below this threshold, necessitating an assessment of their bioaccumulation potential via their K_{OW} , as detailed in Table 6.

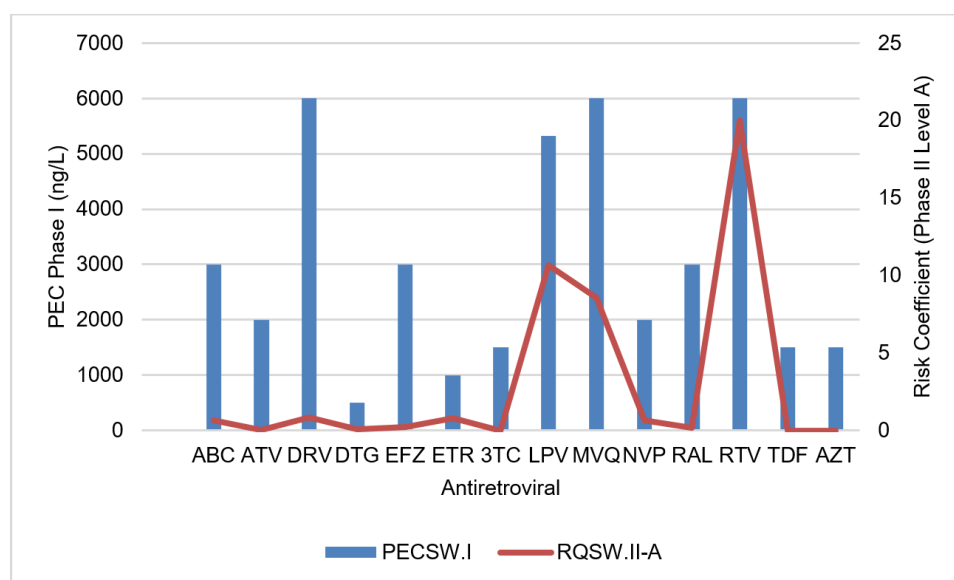
Table 6 Log K_{OW} values for ARVs with PEC_{SW.I.AC} less than 10 ng/L. Source: Marzabal et al. [16]; PubChem [17].

Drug	Log K _{OW}
Etravirine	4.02
Lopinavir	6.27
Maraviroc	5.80
Nevirapine	1.81
Raltegravir	0.40

From Table 6, lopinavir and maraviroc were identified as having bioaccumulative potential, thereby warranting their progression to Phase II analysis within the ERA model [13]. In Phase II - Level A, none of the pharmaceuticals evaluated using the adapted model indicated a significant risk of exposure to aquatic biota. In contrast, lopinavir, maraviroc, and ritonavir produced an RQ greater than one under the standardized model, justifying their advancement to the Phase II - Level B analysis [13]. Finally, at this advanced stage, the PECs for lopinavir, maraviroc, and ritonavir ranged from 47.5 mg/L to 403.6 mg/L - concentrations substantially exceeding the 10 ng/L action limit. This finding, however, was exclusive to the standardized EMEA analysis and was not observed in the BH-specific adaptation analysis.

3.3 ERA Model (2018)

Using the updated 2018 ERA model, it is observed that during Phase I, all pharmaceuticals exhibit PECs exceeding 10 ng/L. The RQ subsequently surpasses 1 for lopinavir, maraviroc, and ritonavir (Figure 3). These three substances, therefore, warrant progression to Phase II of the ERA model [14]. Nevertheless, this advanced analysis was only feasible for lopinavir, as it was the sole compound for which all requisite data were available. This analysis ultimately yielded a PEC value substantially below the nanogram-per-liter threshold.

**Figure 3** Initial predicted environmental concentration (PEC_{SW.I}) and Risk Coefficient (RQ_{SW.II-A}) of Phase II Level A. Source: Authors.

Although not mandated by the model's protocol, PECs were additionally calculated at Level II for atazanavir, efavirenz, and raltegravir. These calculations yielded values ranging from nanogram to picogram per liter concentration, as detailed in Table 7. Consequently, the concentrations of these compounds are notably low, suggesting a minimal probability of potential contamination of the aquatic bodies in Belo Horizonte within the specific case under investigation.

Table 7 Results of applying the ERA model [14]. Source: Authors.

ARV	PEC _{SW,II} (ng/L)	RQ _{SW,II-B}
Atazanavir	$2.81 * 10^{-15}$	$4.11 * 10^{-14}$
Efavirenz	$5.47 * 10^{-12}$	$3.88 * 10^{-10}$
Lopinavir	$4.51 * 10^{-18}$	$8.30 * 10^{-15}$
Raltegravir	$1.16 * 10^{-12}$	$7.016 * 10^{-11}$

3.4 Population Projection

Regarding the population modeling, predicated on the adjusted logistic curve equation, the resultant MAE was approximately 44,000 inhabitants. This deviation corresponds to 1.8% of the 2010 population of Belo Horizonte. Furthermore, the suitability of the model, as quantified by the R^2 coefficient (coefficient of determination), was exceptionally high at 0.99. Figure 4 delineates the projected values for the low, median (average), and high population scenarios.

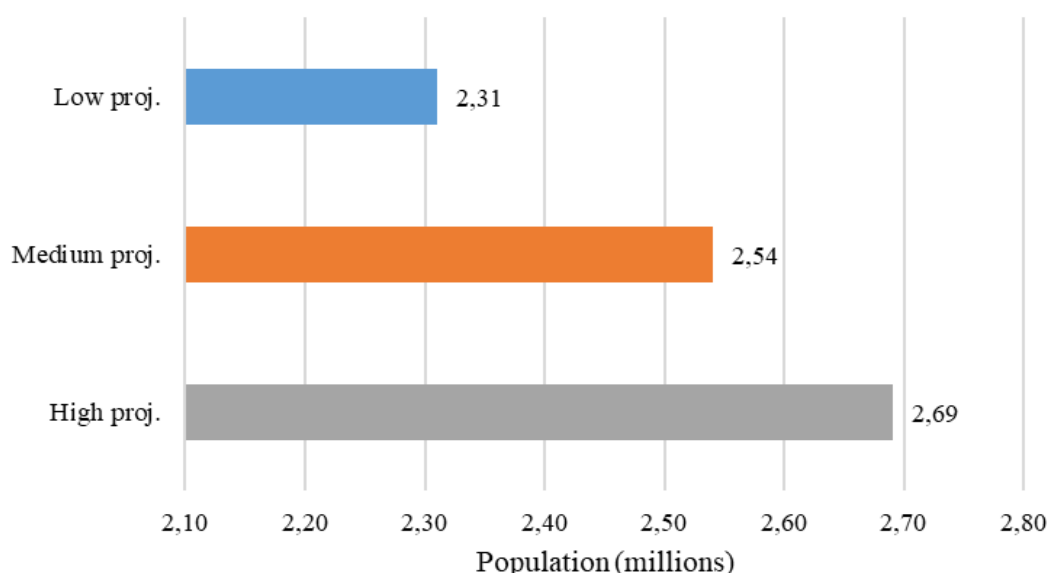


Figure 4 Low, medium and high projection scenarios for the population of Belo Horizonte in 2050*. Source: Authors. * Take the comma as a point.

Given that the estimated population of Belo Horizonte for 2021 was 2.53 million inhabitants [15], the data presented in Figure 4 illustrates a projected population for 2050 that is effectively equivalent to, or potentially less than, the 2021 figure. Furthermore, even the “high projection” scenario, which represents overestimated growth, does not indicate a population substantially exceeding the expected baseline.

3.5 Monte Carlo Simulation

Recognizing that the expansion of sanitary sewerage infrastructure is contingent upon a multitude of economic, social, political, and environmental determinants, yet given the substantial temporal horizon between the present study and 2050, an assumption was made that the $WASTE_{collected}$ parameter for 2050 would equal 1. This value signifies a position of complete (100%) municipal wastewater collection coverage within Belo Horizonte by that year.

Figure 5 depicts the sample mean ($\bar{x}$) and the sample standard deviation (μ) from the four convergence tests (conducted with 100, 1,000, 10,000, and 20,000 events) for the “inhabitants” (population) and $WASTE_{Inhab.AC}$ parameters are foundational variables. As illustrated, the population variable exhibits a smaller μ at 10,000 events, whereas the $WASTE_{Inhab.AC}$ variable demonstrates a smaller standard deviation μ at 20,000 events.

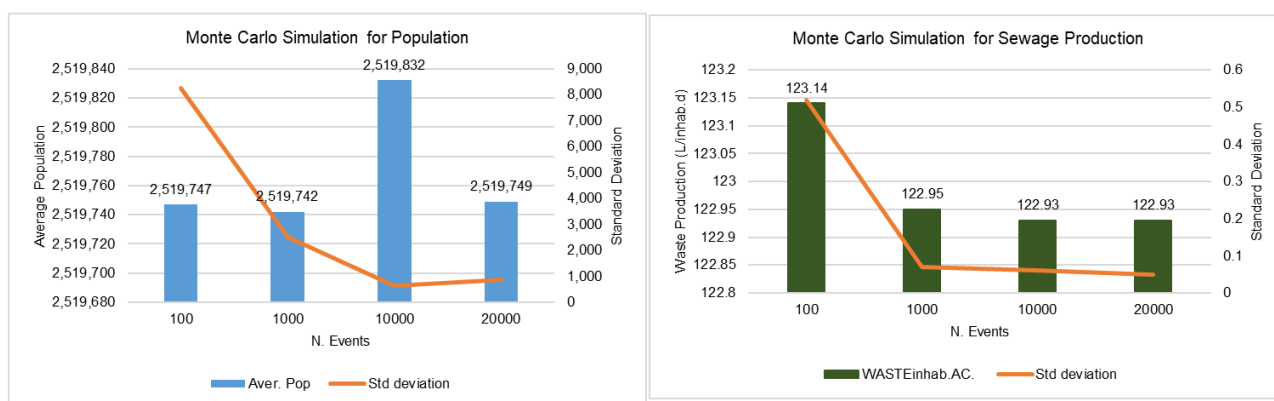


Figure 5 $\bar{x}$ (sample mean) and μ (standard deviation) of the events generated for the MCS convergence analysis referring to Inhabitants (Population) and the volume of sewage per capita per day in Belo Horizonte ($WASTE_{Inhab.AC}$). Source: Authors.

Regarding the convergence analysis, it was observed that the sample mean ($\bar{x}$) for $WASTE_{Inhab.AC}$ remained consistent between the 10,000 and 20,000 event scenarios, and the disparity in the standard deviation (μ) between these two analyses was minimal. This observation, along with the findings for the Population variable, affirmed the stability of the model. Therefore, based on this convergence assessment, 10,000 events were deemed sufficient for this research.

Upon executing the MCS for 10,000 events, considering the 2006 ERA model [13] with both standardized and adapted values, the contamination potential was evaluated. The 14 ARVs studied under the adapted ERA model demonstrated a low capacity for contaminating the aquatic bodies of Belo Horizonte, based on a constant patient contingent in 2050. Conversely, under the standardized model, Phase I results indicated that all pharmaceuticals exceeded 10 ng/L. Consequently, the RQ in Phase II - Level A surpassed 1 for all compounds. In Phase II - Level B, nearly all analyzed pharmaceuticals exhibited refined concentrations exceeding 10 ng/L, the singular exception being abacavir, as extant literature suggests this agent is completely eliminated during wastewater treatment processes [8].

Pertaining to the MCS results for the 2018 ERA model, the stochastic parameters employed were identical to those used for the 2006 ERA simulation, and 10,000 events were likewise executed. Projections for 2050 indicated that all pharmaceuticals would yield an initial PEC_{SW} exceeding 10

ng/L. Furthermore, abacavir, darunavir, etravirine, lopinavir, maraviroc, and ritonavir demonstrated the potential to yield an initial $RQ > 1$, signifying a priori environmental risk to aquatic biota. This finding is attributable to the exceptionally low PNEC values for these compounds, which serve as the denominator in the RQ calculation (Equation 2) - registering 0.0045, 0.0072, 0.0141, 0.0005, 0.0007, and 0.0003 ng/L, respectively. Progression to Phase II of the ERA model [14] was constrained by data deficiencies, specifically the absence of $K_{OC,SOIL}$ values, permitting the analysis of only a subset of these pharmaceuticals. Nonetheless, among those compounds fully evaluated, none were projected to pose a potential to inflict environmental harm on the aquatic bodies of Belo Horizonte.

3.6 Sensitivity Analysis

The Sensitivity Analysis (SA) results indicate uniform values across the pharmaceuticals. This uniformity is a direct consequence of the dependence of the Stability Index (SI) equation on each discrete variable under analysis, as the methodology employed the *ceteris paribus* principle - wherein one variable is modified while all others are held constant.

Consequently, for the $WASTE_{inhab}$ variable, the EI was 0.596 for atazanavir, efavirenz, lopinavir, and raltegravir. For the "Inhab." (Population) variable, the EI was 0.595 for all aforementioned medicines. Similarly, the $F_{stp.water}$ variable yielded a uniform EI of 1. The $F_{excreta}$ parameter was the sole exception, presenting an EI of 1 for most drugs but a distinct value for efavirenz (1.323), as detailed subsequently.

The $PEC_{SW,II}$ equation exhibits the most incredible sensitivity to the $F_{excreta}$ parameter (the percentage of drug excretion), which was 27% for atazanavir, 83.8% for etravirine, 22% for lopinavir, and 10.5% for raltegravir [17, 18, 22-24]. Efavirenz registered the highest EI (1.323) for the $F_{excreta}$ parameter. This necessitated adjusting the model to set the minimum boundary of this variable to zero, since a negative excretion value is physically impossible. This finding suggests that an ideal mitigation strategy would be to enhance the pharmacological enhancement of medicines to increase their metabolic biotransformation within the human body.

Equally impactful in the $PEC_{SW,II}$ calculation is the $F_{stp.water}$ variable, corresponding to the pharmaceutical fraction persisting in the post-treatment effluent. Therefore, enhancing wastewater treatment processes by implementing advanced technologies to destroy recalcitrant compounds is a viable solution. It is crucial to underscore the importance of dedicated research into such treatments, as the resultant degradation byproducts may potentially exhibit greater toxicity than the parent active ingredients.

4. Discussion

The 2018 ERA model offers a more robust framework for modeling the environmental compartments implicated in aquatic contamination by pharmaceuticals. This enhanced assertiveness stems from its inclusion of parameters beyond the 2006 model, namely: the drug concentration in raw sewage, the concentration in treated effluent, and the adsorption factor to suspended matter. The latter parameter, in turn, integrates the organic carbon-water partition coefficient (K_{OC}), the fraction of organic carbon in suspended solids, and the solid-water partition coefficient for suspended matter.

Consequently, the values derived from the Phase II - Level B analysis of the 2018 ERA model are significantly lower than those obtained at the equivalent stage of the 2006 ERA model. While the

2006 model yielded results in the milligram range, the 2018 model extends to the attogram (10^{-18}) range.

A general analysis of the ERA application revealed a significant lacuna in the literature regarding essential environmental effects data for these pharmaceuticals. This gap is particularly pronounced for the K_{OC} variable, which was unavailable for 71% of the ARVs analyzed. This data deficiency reduces the model's accuracy in predicting ARV environmental behavior. Specifically, in the 2006 ERA model, its absence precluded the completion of calculations for the respective compounds. In the 2018 ERA model, the lack of this variable necessitates defaulting the suspended matter absorption factor to 1, which, in turn, directly impacts the final $PEC_{SW,II}$.

Regarding the MCS, it is crucial to note that the model assumed static ARV consumption levels over time in Belo Horizonte. This assumption was necessary as it was not feasible to estimate the future patient population; while aggregate consumption quantity is known, the specific population served is not.

The SA of the ERA model highlights two primary mitigation pathways. The first involves enhancing in vivo drug metabolism, a factor contingent on individual usage patterns. The second, more actionable approach is to improve wastewater treatment systems, as a significant fraction of the analyzed pharmaceuticals persists in treated effluent. In some instances, effluent concentrations may even exceed influent concentrations, a phenomenon attributed to the reversion of metabolites back into Active Pharmaceutical Ingredients (APIs). Several studies have focused specifically on ARV treatment efficacy, notably Souza et al. [10], Adedapo et al. [9], and Bhembe [5]. This focus is justified, as ARVs are known to be highly detrimental to various non-target organisms, as elucidated by Ncube et al. [8], Oyinkansola [20], Kowalser et al. [25], Bhembe [5], and Ntombikayise and Ndeke [26].

The data generated by the ERA model are of considerable value, guiding the scientific community by identifying which pharmaceuticals pose the most significant risk of harm to aquatic biota and the broader food web. In this context, numerous authors have employed the EMEA [13] ERA framework for risk analysis, predominantly executing Phase I and Phase II - Level A assessments, as seen in the work of Mingues et al. [27], Escher et al. [28], Daouk [29], Laranjeira [7], Marzabal et al. [16], and Cid [30].

Thus, this study implies that, according to the 2018 ERA Model, none of the antiretroviral drugs administered in BH through 2020 represent an environmental risk to its rivers. Conversely, the 2006 ERA Model - which may be considered more conservative - suggests that lopinavir, maraviroc, and ritonavir may inflict harm upon aquatic fauna. It is noteworthy that other studies have classified lopinavir and ritonavir as "maximum priority" compounds due to their $RQ > 10$, a finding corroborated herein [31, 32].

The calculated PECs for these substances ranged from 47.5 mg/L to 403.6 mg/L, exceeding the typical ng/L to μ g/L concentrations reported for most pharmaceuticals in surface waters globally [33]. Such exceptionally high PECs are likely attributable to a confluence of factors: high consumption rates, inherent persistence due to molecular design, and inefficient removal by conventional wastewater treatment processes. The case of these three ARVs epitomizes the core challenges discussed: critical data gaps (e.g., missing K_{OC} values obscuring their true environmental fate) and model limitations (e.g., static consumption assumptions) converge to identify these compounds as priorities for regulatory attention and ecological monitoring.

Therefore, while the overarching model contains uncertainties, the pronounced risk signal for lopinavir, maraviroc, and ritonavir is robust, highlighting a tangible, localized threat to aquatic ecosystems that necessitates urgent mitigation strategies.

The data gaps identified in this investigation are not an isolated phenomenon but rather a recurring challenge in the ERA of pharmaceuticals globally. Similar reviews have consistently reported a critical lack of key environmental fate parameters [6, 33]. The situation for ARVs, however, appears to be particularly acute. While nations with mature ecological monitoring programs (e.g., the European Union) generate proprietary data for high-volume drugs, ARVs are frequently overlooked due to more localized consumption patterns (low- and middle-income countries). This disparity underscores a global imbalance in environmental research: pharmaceuticals prevalent in high-income nations are better characterized than those essential to public health in developing and underdeveloped countries, which often possess less robust wastewater treatment infrastructure [34].

The reliance on default model values in the absence of experimental data, as necessitated in the 2018 ERA model application, is a common practice that introduces significant uncertainty into risk assessments. Our finding that this practice likely yields an overestimation for certain ARVs aligns with studies on other polar organic contaminants. Default assumptions for pharmaceuticals are known to both over- and under-predict environmental concentrations, contingent upon the specific properties of compounds.

This consistency across disparate geographical and therapeutic contexts reinforces that our results are not a methodological anomaly but rather reflect a systemic issue in predictive environmental toxicology. This emphasizes the urgent need for targeted experimental studies to supplant generalized assumptions with compound-specific data, a critical point recently articulated by Patel et al. [35] in their review of pharmaceutical prioritization approaches.

To address these critical data gaps and mitigate the potential environmental impact of ARVs, a multi-faceted approach is required. First, we strongly recommend that environmental and health regulatory agencies mandate the submission of fundamental environmental fate data (including K_{oc} , biodegradation half-life, and aquatic toxicity) during the marketing authorization process for new ARVs, mirroring the precedent set by the EMA [14]. For medications, we propose establishing targeted research funding to prioritize the experimental determination of these parameters for high-consumption compounds, analogous to the "watch list" mechanism implemented under the EU Water Framework Directive [36].

Furthermore, given the inherent limitations of conventional wastewater treatment plants in removing complex synthetic molecules, technological upgrades are imperative. Policymakers should incentivize the implementation of advanced (tertiary) treatment technologies, particularly in high-burden areas. Techniques such as Advanced Oxidation Processes (AOPs) - e.g., ozonation, and UV/H₂O₂ - have demonstrated high degradation efficacy (>88%) for certain ARVs [37]. Similarly, membrane filtration (e.g., reverse osmosis, nanofiltration) has proven highly effective at removing emerging contaminants [38]. Investment in these technologies addresses not only ARVs but also the entire spectrum of emerging contaminants, thereby protecting aquatic ecosystems and public health.

Ultimately, integrating "green pharmacy" principles into drug design and adopting a "One Health" approach in public policy are essential long-term strategies to minimize the environmental footprint of essential medicines [39].

5. Conclusion

In conclusion, this study unequivocally identifies lopinavir, maraviroc, and ritonavir as the highest-priority ARVs of environmental concern in the studied region. Their exceptionally high PECs signal a potential for significant ecological risk that must not be overlooked.

Therefore, these specific compounds must be the primary targets for immediate, concerted action, encompassing: (1) the urgent experimental determination of their environmental fate and toxicity parameters; (2) the implementation of advanced wastewater treatment technologies at key discharge points; and (3) their inclusion in future environmental monitoring campaigns within Brazilian aquatic systems.

The utilization of standard (default) values in the ERA model leads to an overestimation of the PEC when compared with the application of site-specific values for the studied municipality. Moreover, the model does not explicitly account for pseudo-persistent substances, potentially leading to a misinterpretation of the actual environmental phenomena. While the continuous environmental introduction of a readily degradable (non-persistent) pharmaceutical may not, per se, pose a concern, the failure of the model to differentiate this from actual persistence could lead to erroneous conclusions. Addressing this limitation is crucial for ensuring a more accurate and comprehensive environmental impact assessment.

Finally, it is recommended that the calculations herein be refined as new scientific data become available. It is further recommended that the forecasting capability of the MCS scenarios presented be validated through future estimations. As previously articulated, there is an urgent imperative for increased investment in treatment technologies capable of removing recalcitrant and pseudo-persistent pollutants from wastewater. This necessity is predicated on the global environmental concern posed by these compounds, particularly lopinavir, maraviroc, and ritonavir, as demonstrated in this and other research endeavors.

Author Contributions

All authors, Míriam de Fátima Soares, Marcos Paulo Gomes Mol, and Frederico Keizo Odan, contributed to the study conception and design. Material preparation and data collection were performed by Míriam de Fátima Soares. All authors, Míriam de Fátima Soares, Marcos Paulo Gomes Mol, and Frederico Keizo Odan, performed analysis. The first draft of the manuscript was written by Míriam de Fátima Soares and all authors commented on previous versions of the manuscript. All authors, Míriam de Fátima Soares, Marcos Paulo Gomes Mol, and Frederico Keizo Odan, read and approved the final manuscript.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

AI-Assisted Technologies Statement

During the writing process of this article, the authors used artificial intelligence-assisted tools, specifically ChatGPT (OpenAI) and Gemini (Google), solely to enhance the readability and linguistic clarity of the manuscript. These tools were not employed to generate original ideas or to analyze data or results. All intellectual content and scientific contributions are the sole responsibility of the authors, in accordance with the research and publication ethics guidelines established by LIDSEN.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Supplementary Information.
2. Table S1: Variables used in the 2006 and 2018 ERA model.

References

1. Prefeitura de Belo Horizonte. Plano Municipal de Saneamento de Belo Horizonte: 2016/2019 [Internet]. Belo Horizonte, Brasil: Prefeitura de Belo Horizonte; 2016. Available from: <https://prefeitura.pbh.gov.br/sites/default/files/estrutura-de-governo/obras-e-infraestrutura/PMS%202016%20-%202019%20%E2%80%93Volume%20I%20%E2%80%93%20Texto.pdf>.
2. IBGE. Cidades e Estados: Brasil [Internet]. Rio de Janeiro, Brazil: IBGE; 2025. Available from: <https://www.ibge.gov.br/cidades-e-estados>.
3. Trata Brasil. Ranking do Saneamento 2025. Esgoto [Internet]. Trata Brasil; 2025. Available from: <https://tratabrasil.org.br/ranking-do-saneamento-2025/>.
4. Minas Gerais. Painel Esgotamento Sanitário e Abastecimento de Água – dados [Internet]. Power BI; 2021. Available from: <https://app.powerbi.com/view?r=eyJrIjojODMyZTRjZTMtNmM5My00ODExLWJjMTUtYzZmNmVIYjFjOTE1liwidCI6IjE2Y2ZDU1LTA1NjgtNDhkZS05YzJhLWE5ZmQxZTMwYjk0MSJ9&pageName=ReportSection281174709ee03bf5aba82021>.
5. Bhembe YA. Photodegradation of a selected antiretroviral drug from South Africa's effluent with a heterostructure of few layer black phosphorus-niobium oxide nanoparticles (FL-BP/Nb₂O₅). Johannesburg, South Africa: University of Johannesburg; 2020.
6. Liu Q, Feng X, Chen N, Shen F, Zhang H, Wang S, et al. Occurrence and risk assessment of typical PPCPs and biodegradation pathway of ribavirin in wastewater treatment plants. Environ Sci Ecotechnol. 2022; 11: 100184.
7. dos Santos Laranjeira DRA. Avaliação do risco ambiental da fluoxetina em sedimentos marinhos para invertebrados aquáticos. São Paulo, Brazil: University of São Paulo; 2019.

8. Ncube S, Madikizela LM, Chimuka L, Nindi MM. Environmental fate and ecotoxicological effects of antiretrovirals: A current global status and future perspectives. *Water Res.* 2018; 145: 231-247.
9. Adeola AO, Forbes PB. Antiretroviral drugs in African surface waters: Prevalence, analysis, and potential remediation. *Environ Toxicol Chem.* 2022; 41: 247-262.
10. Souza SJ, Lobo TM, Sabino AL, Oliveira SB, Costa OS. Decomposição dos antirretrovirais lamivudina e zidovudina pelo processo fotofenton assistido no efluente de indústria farmacêutica. *Rev Process Químicos.* 2010; 4: 59-67.
11. Abafe OA, Späth J, Fick J, Jansson S, Buckley C, Stark A, et al. LC-MS/MS determination of antiretroviral drugs in influents and effluents from wastewater treatment plants in KwaZulu-Natal, South Africa. *Chemosphere.* 2018; 200: 660-670.
12. Kulišťáková A. Removal of pharmaceutical micropollutants from real wastewater matrices by means of photochemical advanced oxidation processes-A review. *J Water Process Eng.* 2023; 53: 103727.
13. EMEA. Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 2) [Internet]. London, UK: European Medicines Agency; 2006. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf.
14. EMEA. Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 2) [Internet]. London, UK: European Medicines Agency; 2018. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf.
15. IBGE. Cidades e Estados: Belo Horizonte [Internet]. Rio de Janeiro, Brazil: IBGE; 2025. Available from: <https://www.ibge.gov.br/cidades-e-estados/mg/belo-horizonte.html>.
16. de Freitas Marzabal AL, Roveri V, de Freitas MS, Toma W, Guimarães LL. Antiretroviral drugs: Predicted environmental concentration and ecological risk Assessment in Sewage Treatment Plants in Cubatão, São Paulo, Brazil. *Res Soc Dev.* 2022; 11. doi: 10.33448/rsd-v11i4.27595.
17. PubChem. Lopinavir (Compound) [Internet]. Bethesda, MD: National Library of Medicine (US), National Center for Biotechnology Information; 2004. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/92727#section=Solubility>.
18. DrugBank. Small Molecule Drugs [Internet]. Alberta, Canada: DrugBank; 2025. Available from: <https://go.drugbank.com/drugs>.
19. United Nations. Department of Economic and Social Affairs Population Division: World Population Prospects 2019 [Internet]. New York, NY: United Nations; 2019. Available from: https://population.un.org/wpp/assets/Files/WPP2019_Highlights.pdf.
20. Omotola EO, Genthe B, Ndlela L, Olatunji OS. Environmental risk characterization of an antiretroviral (ARV) lamivudine in ecosystems. *Int J Environ Res Public Health.* 2021; 18: 8358.
21. Empresa Brasileira de Serviços Hospitalares. Centro de Testagem e Aconselhamento [Internet]. Brazil: gov.br; 2020. Available from: <https://www.gov.br/ebserh/pt-br/hospitais-universitarios/regiao-norte/hdt-uft/saude/centro-de-testagem-e-aconselhamento>.
22. Fung HB, Stone EA, Piacenti FJ. Tenofovir disoproxil fumarate: A nucleotide reverse transcriptase inhibitor for the treatment of HIV infection. *Clin Ther.* 2002; 24: 1515-1548.

23. Iwamoto M, Wenning LA, Petry AS, Laethem M, De Smet M, Kost JT, et al. Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. Clin Pharmacol Ther. 2008; 83: 293-299.
24. Heald AE, Hsyu PH, Yuen GJ, Robinson P, Mydlow P, Bartlett JA. Pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with renal dysfunction. Antimicrob Agents Chemother. 1996; 40: 1514-1519.
25. Kowlaser S, Barnhoorn I, Wagenaar I. Developmental abnormalities and growth patterns in juvenile *Oreochromis mossambicus* chronically exposed to efavirenz. Emerging Contam. 2022; 8: 83-89.
26. Mahaye N, Musee N. Effects of two antiretroviral drugs on the crustacean *Daphnia magna* in river water. Toxics. 2022; 10: 423.
27. Minguez L, Pedelucq J, Farcy E, Ballandonne C, Budzinski H, Halm-Lemeille MP. Toxicities of 48 pharmaceuticals and their freshwater and marine environmental assessment in northwestern France. Environ Sci Pollut Res. 2016; 23: 4992-5001.
28. Escher BI, Baumgartner R, Koller M, Treyer K, Lienert J, McArdell CS. Environmental toxicology and risk assessment of pharmaceuticals from hospital wastewater. Water Res. 2011; 45: 75-92.
29. Daouk S, Chèvre N, Vernaz N, Bonnabry P, Dayer P, Daali Y, et al. Prioritization methodology for the monitoring of active pharmaceutical ingredients in hospital effluents. J Environ Manage. 2015; 160: 324-332.
30. Cid RS. Estudo ecotoxicológico de medicamento antirretrovirais: Concentrações ambientais estimadas e efeitos biológicos em ouriço-do-mar (*Echinometra lucunter*). Santos, Brazil: Santa Cecília University; 2020.
31. Souza-Silva G, Bispo VA, Alcantara MD, Vieira Martins Starling MC, de Souza CR, Jardim LT, et al. Aquatic ecotoxicology of antiretrovirals: A review. Environments. 2025; 12: 384.
32. Ngwenya P, Musee N. Modelling ecological risks of antiretroviral drugs in the environment. Environ Chem Ecotoxicol. 2023; 5: 145-154.
33. Aus der Beek T, Weber FA, Bergmann A, Hickmann S, Ebert I, Hein A, et al. Pharmaceuticals in the environment-Global occurrences and perspectives. Environ Toxicol Chem. 2016; 35: 823-835.
34. Gwenzi W, Simbanegavi TT, Rzymski P. Household disposal of pharmaceuticals in low-income settings: Practices, health hazards, and research needs. Water. 2023; 15: 476.
35. Patel M, Kumar R, Kishor K, Mlsna T, Pittman Jr CU, Mohan D. Pharmaceuticals of emerging concern in aquatic systems: Chemistry, occurrence, effects, and removal methods. Chem Rev. 2019; 119: 3510-3673.
36. European Commission. Commission Implementing Decision (EU) 2020/1161 of 4 August 2020 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council (notified under document number C(2020) 5205) (Text with EEA relevance) [Internet]. European Union; 2022. Available from: https://eur-lex.europa.eu/eli/dec_impl/2020/1161/oj.
37. de Lucena AL, Napoleão DC, da Silva HV, da Rocha Santana RM, Ribeiro BG, Duarte MM. Degradation of the pharmaceuticals lamivudine and zidovudine using advanced oxidation processes. Sci Nat. 2020; 42. doi: 10.5902/2179460X40968.
38. Patel HK, Kalaria RK, Jokhakar PH, Patel CR, Patel BY. Removal of emerging contaminants in water treatment by an application of nanofiltration and reverse osmosis. In: Development in

wastewater treatment research and processes. Amsterdam, Netherlands: Elsevier; 2022. pp. 385-400.

39. Carresi C, Pauletto M, Fiore E, Musolino V, Britti D. Green veterinary pharmacology and toxicology: A “one health” approach milestone. *Front Vet Sci*. 2024; 11: 1476877.