

Analysis of opioid analgesics consumption in Africa: a longitudinal study from a 20-year continental perspective

universite **PARIS-SACLAY**

Yacine Hadjiat, Jallal Toufiq, Christian Ntizimira, Lars Arendt-Nielsen, Benoit Burucoa, Erwan Treillet, Nicolas Authier, Serge Perrot

National Institute of Health and Medical Research (INSERM, U987), Paris-Saclay University of Medicine, Dubai Health Care City, United Arab Emirates (Y Hadjiat); Rabat Faculty of Medicine, Mohammed V University, Rabat, Morocco (Prof J Toufiq MD); International Narcotics Control Board, United Nations, Vienna, Austria (Prof J Toufiq); African Center for Research on End-ofLife Care, Kigali, Rwanda (C Ntizimira MD); Center for Neuroplasticity and Pain (CNAP)/SMI, Department of Health Science and Technology, School of Medicine, Aalborg University, Gistrup, Denmark (Prof L Arendt-Nielsen), Clinical Institute, Aalborg University Hospital, Aalborg, Denmark; French International Federation of Palliative Care (FISP), Geneva, Switzerland (B Burucoa MD); Pain Without Borders, Paris, France (E Treillet); Pain Management and Palliative Care Unit, Colmar, France (E Treillet); Pain Management and Palliative Care Unit, APHP Lariboisiere Hospital, Paris, France (E Treillet); Université Clermont Auvergne, CHU Clermont-Ferrand (INSERM 1107), Neuro-Dol, Service de Pharmacologie Médicale, Centres Addictovigilance et Pharmacovigilance, Centre for Analgesic Drugs (OFMA), Clermont-Ferrand, France (Prof N Authier); Pain Management Department, Cochin Hospital, Paris Cité University, Paris, France (Prof S Perrot)

Abstract

Opioids, which include pain relievers such as morphine, are recognised by WHO as an essential medicine. They can alleviate a substantial proportion of what the Lancet commission on palliative care and pain relief called serious health-related suffering. In2016about 25·7 million people died in need of palliative care due to serious health-related suffering of whom about 80% lived in low-income and middle-income countries (LMICs) with limited access to pain management care. By 2060, it is estimated that 48 million people will die needing palliative care, 83% of whom will reside in LMICs. This projection represents an 87% increase relative to 2016

On the other hand, the extra-medical use of opioids, referring to illicit use or misuse without a prescription by a health-care professional, is escalating and becoming a substantial public health issue in many countries. Owing to their potentially highly addictive nature, opioids can lead to serious medical complications, including death. The number of deaths caused by opioidrelated overdoses in the USA increased from 49 860 in 2019 to 81 806 in 2022, highlighting the escalating opioid crisis. The crisis also carries a significant economic burden and heavily impacts families and communities, causing broken relationships due to opioid addiction, reduced economic productivity, and increased crime rates. The stigma associated with opioid misuse can negatively affect their essential medical use for pain management

There is an important inequity in access to opioids for those in need between countries. An analysis of data on opioid analgesics sales from hospital and retail settings estimated that, between 2009 and 2019, the median opioid consumption rate in highincome countries (HICs) was 345·1 morphine mg equivalents per 1000 inhabitants per day, versus 23·6 in upper-middle-income countries, and 8·3 in low-income and lower-middle income countries. In 2023, WHO published a report on access to morphine for medical use, highlighting the global inequity in distribution and the fact that this pattern does not correlate with the actual demand for medical pain management. In 2021, 33 115 kg of morphine was distributed globally for medical and scientific purposes, with about 80% of it allocated to HICs, mainly in the WHO Region of the Americas and the European Region.

Introduction

Opioid analgesics are essential in managing acute and some chronic pain conditions, particularly cancer and palliative care. For cancer pain, no medication other than opioid analgesics can offer immediate and effective pain relief. WHO has listed opioid analgesics as essential medicines for pain and palliative care. Globally, opioid consumption has doubled every 10 years. However, 92% of the available opioids were consumed by only 17% of the world's population who reside in high-income countries. The remaining 8% of opioids were consumed in low income and middle-income countries, which constitute 83% of the global population. These findings highlight the disparity in global opioid consumption, with certain regions experiencing excessive usage whereas others grapple with inadequate consumption of opioid analgesics. Therefore, it is inaccurate to portray global opioid consumption as a homogeneous entity, and it is crucial to underscore the unique challenges faced by low-income countries such as those in Africa to ensure equitable access to opioids for pain treatment. In Africa, in patients with moderate pain that is not adequately controlled with regular non-steroidal anti-inflammatory drugs or paracetamol, opioids such as tramadol, codeine, or low-dose morphine are indicated. If the pain progresses into a more severe form, potent opioids such as morphine, oxycodone, hydromorphone, and fentanyl are then indicated. However, pain management in Africa faces a myriad of challenges, with the shortage of essential opioid formulations particularly hindering effective palliative care. Market barriers and bureaucratic processes impede timely access to opioids, which is further exacerbated by stringent prescription policies. Moreover, health-care professionals in Africa often opt for non-opioid analgesics as a first-line treatment of severe pain over essential opioids. Because most African countries fall in the low-income and lower middle-income category, opioids are often unaffordable for both individual patients and health-care institutions. The prevailing stigma surrounding pain endurance, palliative medicine, opiophobia, and the fear of opioid use also further complicates the situation.

> Evidence before this study Before conducting this study, we gathered evidence from the conducted a literature search within the relevant field. We searched PubMed on Nov 30, 2023 for all article types published and in the French-speaking sub-regions. Moreover, the between database inception and Nov 30, 2023, with no language restrictions. A full list of search terms is included in appendix 2 (p 4). Existing knowledge about global trends in opioid analgesic use stemmed from two previous studies, overing the periods from 2001 to 2013, and 2015 to 2019. These studies indicated a substantial increase in global opioid analgesic use, which was primarily driven by increases in highincome countries. However, countries with low-income and middle-income levels, such as African nations, experienced persistently low consumption, resulting in huge global disparities. Despite the call for action from the INCB, no study has specifically focused on the African context within the past 20 years, incorporating sub-analyses of individual substances, cancer incidence, cancer mortality, and income levels.

In our study encompassing 57 African countries from 1999 to and political determinants driving these inequities. Urgent 2021, we have provided specific and up-to-date data and analysis of opioid analgesic consumption in all African countries multifaceted challenges faced by these nations, urging further based on INCB data. Our findings have revealed a low and research, and tailored sub-regional and local solutions to stagnant trend in opioid consumption across Africa during the address the overarching predicament across Africa. past two decades. The analysis of individual opioid substances

also highlights a slight increase in morphine consumption during the last two decades. Sub-analyses of opioid countries with low-income and lower-middle-income levels during the past 20 years is particularly alarming given the ongoing increases in cancer incidence and mortality, analgesics for palliative care when indicated.

Despite the initial call for action in 2016 in a study by consumption persists in African nations, showing minimal analysis further highlights pronounced disparities between African countries, particularly when considering the increasing cancer incidence and mortality, in low-income countries versus high-income countries, and in French-speaking versus Englishattention and concerted efforts are imperative to address the

Methodology

Data sources: We performed a secondary analysis on the most recent opioid consumption data in African countries. The opioid consumption data from 1999 to 2021 was obtained from the Narcotics Control and Estimates Section of the International Narcotics Control Board (INCB) on Nov 17, 2023. According to the INCB and the 1961 Convention (Article 1), drug consumption is recorded when the drug has been supplied to any person or enterprise for retail distribution, medical use, or scientific research. Therefore, the consumption data provided by governments in each country, as per the requirements of the 1961 Convention (Article 13 and 20), represent the drug distribution from wholesale to retail but not necessarily the actual administration of the

substances.18 This information was then verified by the INCB using data from export and import notifications. Among these narcotic drugs, codeine, dextromoramide, dextropropoxyphene, dihydrocodeine, diphenoxylate, dipipanone, ethylmorphine, fentanyl, hydrocodone, hydromorphone, morphine, nicomorphine, pethidine, phenoperidine, pholcodine, piritamide, opium, oxycodone, and tilidine consumption was reported in Africa and analysed in this study. Total population data and income levels of each African country were retrieved from the World Bank, epidemiological data on cancer incidence were extracted from the WHO Global Cancer Observatory (Globocan) database, and data on mortality were from the Institute for Health Metrics and Evaluation, Global Burden of Disease. Ethics approval is not required for this study as there is no direct subject involvement. The research exclusively relies on data from the INCB and other online databases, and no information is disclosed that could identify

Definition of variables: Defined daily doses for statistical purposes (SDDD) is a technical unit of measurement and should not be confused with the prescription dose. SDDD was used because there are no existing internationally agreed standard doses for opioid analgesic prescriptions; hence, SDDD provides an approximate measure of the amount of opioids used and allows for a fair comparison between countries. Opioid use, expressed in SDDD per million inhabitants per day, was calculated with the following formula: annual use divided by 365 days, divided by the population in millions of the country or territory during the year, divided by the defined daily dose. The income level of each African country was defined according to the World Bank's classification into four income groups, which were low-income, lower-middle-income, upper-middle-income, and high income. The classifications were based on the annual gross national income per capita. Cancer incidence was defined as the number of newly diagnosed cases and mortality was defined as the number of deaths during a specific time period. In terms of language spoken, 57 African countries were divided into 24 French-speaking African countries and 33 other African countries.

Statistical analysis: The time trend of opioid consumption was evaluated and assessed in terms of SDDD in all African countries from 1999 to 2021, to establish the extent of use. The total SDDD in the French-speaking countries and other African countries was obtained and plotted into a single graph with all African countries for the sub-regional cluster analysis. For the time-series analysis, the trend of the SDDD from 1999 to 2021 was determined by a researcher observational method, which interprets the goodness-of-fit of the SDDD and decides if the trend is linear or exponential in nature. Subsequently, the results from 1999 to 2021 were then used to generate a predictive line to estimate the future SDDD trends.

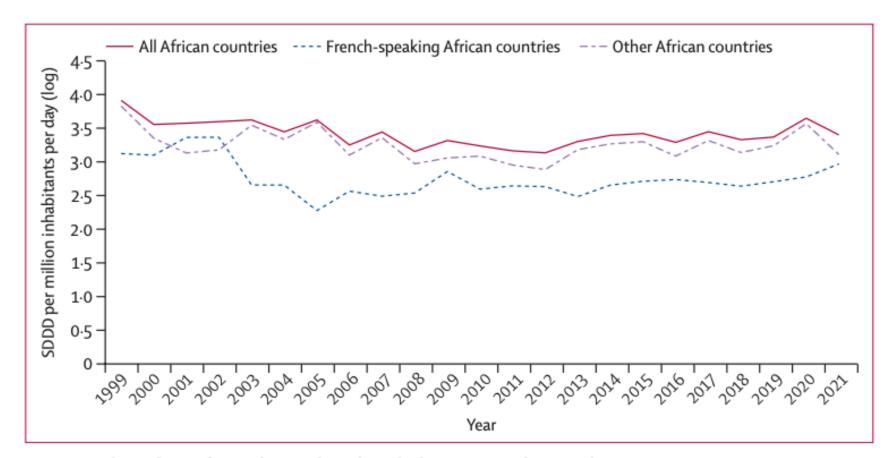


Figure 5: Sub-analysis of opioid SDDD based on the language spoken in Africa A total of 57 African countries are in the All African countries category. There are 24 French-speaking African countries, including 21 Francophone countries and three additional African countries (Algeria, Morocco, and Tunisia) that comprise a large French-speaking population. Other African countries are the remaining 36 African countries that are not part of the French-speaking African countries. Data were obtained from the International Narcotics Control Board. SDDD=defined daily doses for statistical purposes.

Results

During the past few decades, global opioid consumption has doubled every 10 years with North American, Oceania, and west and central European countries reporting very high opioid use, but consumption has remained very low in low-income countries, particularly in Africa. We found that opioid consumption in African countries has remained low and stagnant during the last two decades, from 73 SDDD (95% CI 69–77) in 2001–03, to 29 SDDD (22–36) in 2011–13, and 55 SDDD (32–79) in 2019–21 (figure 1; table). The detailed SDDD for each African country have been presented in the table, whereas heatmaps illustrating the evolution of opioid consumption for the years 2001–03, 2011–13, and 2019–21 are presented here. Next, we analysed the SDDD of individual opioid substances in Africa, to discern the contribution of each substance to the overall consumption trend. Among these substances, morphine and oxycodone consumption showed a gradual increasing trend for the past decade (figure 2). Specifically, in-depth analysis revealed a morphine consumption increase from 735 SDDD in 1999 to 1115 SDDD in 2021. Notably, Saint Helena, Seychelles, South Africa, and Tunisia had a relatively higher morphine SDDD compared with the other African countries whereas oxycodone consumption was mainly reported by South Africa. To ascertain whether the consumption of opioid analgesics in African countries correlates with their income levels, a sub-analysis of SDDD was performed by categorising each African country into low-income, low-middle-income, upper-middle-income, and high-income groups. Our findings revealed a positive association between opioid consumption SDDD and income level (figure 3). Among the upper-middle-income and highincome countries, Mauritius, Seychelles, and South Africa had a relatively higher SDDD, which records 231 SDDD, 239 SDDD, and 827 SDDD opioid consumption in 2021, respectively. Interestingly, despite being a country in the lower-middle-income category, Tunisia had a higher SDDD than most of the upper-middle-income and high-income countries, with an SDDD of 545 in 2021 (appendix 2 pp 7–8). Although cancer incidence and mortality in Africa has consistently risen during the last 20 years (figure 4), the consumption of opioids remains almost unchanged (figure 1). The relationship between cancer incidence and mortality and consumption of opioids in Africa suggests a vast health-care problem: analgesics are not available for cancer pain treatment. Most African countries, excluding South Africa and Saint Helena, exhibit a close proximity to the x-axis, indicating existing cancer incidence and mortality without corresponding access to opioid analgesics (figure 4B). To further explore the interplay between cancer mortality and the trend in consumption of each opioid substance, a time-series analysis was conducted. Among all opioids, we showed that morphine exhibited an increasing consumption trend along with the cancer mortality. Ethnolinguistic diversity is an important determinant of outcomes such as income. Therefore, we performed sub-regional cluster analysis based on language spoken in different regions within Africa. Our results have shown that French-speaking African countries generally exhibited lower SDDD than other African countries throughout most of the analysed time period, except 2000–01 (figure 5). Moreover, when we break the African countries further down into French-speaking African countries, English-speaking African countries, and other African countries, we observed that the SDDD of French speaking African countries remained lower than the English-speaking countries and other African countries (figure S6).



Figure S6: Heatmaps illustration of the opioid consumption evolution throughout the intervals of 2001-2003, 2011-2013, and 2019-2021 in French-speaking African countries (a-c), Englishspeaking African countries (d-f) and other African countries (g-i).

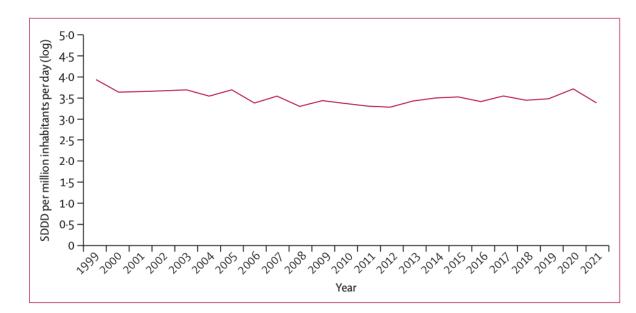


Figure 1: SDDD of opioid analgesics (log) in African countries from 1999 to 2021 Data were obtained from the International Narcotics Control Board. SDDD=defined daily doses for statistical

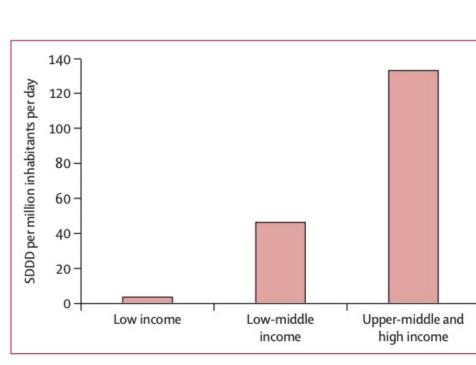


Figure 3: Sub-analysis of opioid SDDD based on the income level in Africa The data for income levels of each African country were retrieved from the World Bank, whereas the SDDD data were obtained from the International Narcotics Control Board. SDDD=defined daily doses for statistical purposes.

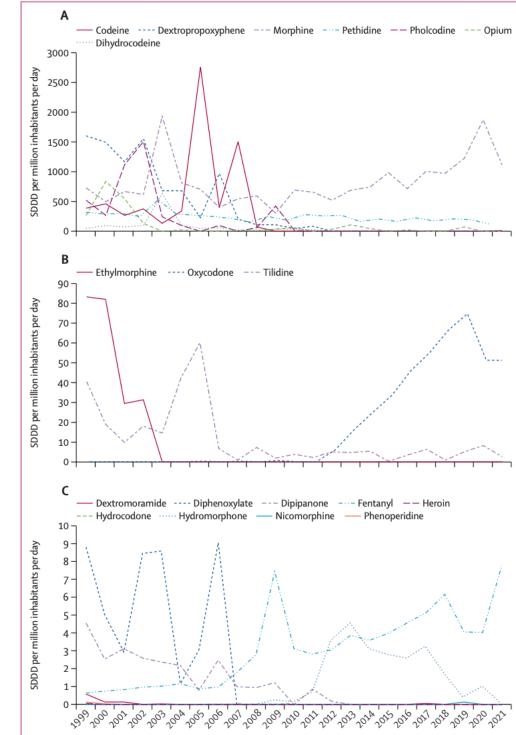


Figure 2: SDDD of individual opioid substances in African countries from 1999 to 2021 (A) Opioid substances with a high SDDD were codeine, dextropropoxyphene, morphine, pethidine, pholcodine, opium, and dihydrocodeine. (B) Opioid substances with a moderate SDDD were ethylmorphine, oxycodone, and tilidine. (C) Opioids with a low SDDD, comprising dextromoramide, diphenoxylate, dipipanone, fentanyl, heroin, hydrocodone, hydromorphone, nicomorphine, and phenoperidine. Data were obtained from the International Narcotics Control Board. SDDD=defined daily doses for statistical purposes.

Conclusion

Despite a huge rise in cancer incidence and mortality, opioid consumption in Africa has remained stagnant for the past two decades. This finding suggests that the availability of opioid analgesics in Africa is still insufficient to cater to the needs of patients receiving cancer pain treatment, probably resulting in unmanaged moderate-to severe pain in many cancer patients during their treatment and end of life. Because cancer incidence is projected to double from 2020 to 2040 and reach 2·1 million, the stagnant opioid consumption level requires urgent attention to prevent the situation from becoming severe, potentially worsening the unmet needs for optimum cancer care. Hence, there is an urgent need for country level policies, programmes, resources, education, and training on palliative care to be in place to improve the overall situation. To our knowledge, for the first time, in this study, we have shown that opioid consumption in African countries has been stagnant at an extremely low and potentially inadequate level during the last two decades. Furthermore, we have shown that in a continent that has little opioid access and use while cancer incidence and mortality has dramatically increased, there are further disparities between subregions with different income levels and languages spoken. Hence, there is an urgent need for more specific research to further explore such disparities and their potential cultural, economic, and political context to design more tailored solutions to overcome the impediments and facilitate progress towards better availability and use of opioids, especially in cancer care and end-of-life care.

1 International Association for the Study of Pain. Opioids for pain management. 2018. https://www.iasp-pain.org/advocacy/iaspstatements/opioids-for-pain-management/ (accessed June 9, 2023). 2 WHO. WHO Model List of Essential Medicines. 2023. https://iris. who.int/bitstream/handle/10665/371090/WHO-MHP-HPS-EML2023.02-eng.pdf?sequence=1 (accessed May 9, 2024). 3 Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. Lancet 2016; 387: 1644–56. 4 Zin CS. Ten years of strong opioid analgesics consumption in Malaysia and other southeast Asian countries. J Pharm Bioallied Sci 2020; 12: S846–51.
5 South African Cancer Pain Working Group. Guide to the treatment of cancer pain in South Africa, 2015. https://sahivsoc.org/Files/ Guidetotreatmentofcanc 6 Yao JS, Kibu OD, Asahngwa C, et al. A scoping review on the availability and utilization of essential opioid analgesics in SubSaharan Africa. Am J Surg 2023; 226: 409–21.

Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1736–88. 8 World Bank. Total population. 2023. https://data.worldbank.org/ indicator/SP.POP.TOTL (accessed Feb 15, 2024). 9 Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol 2001; 2: 533–43.

10 The Global Cancer Observatory. Africa: Globocan 2020, 2021. https://gco.iarc.fr/today/data/fa 11 Institute for Health Metrics and Evaluation, Global Burden of Disease. Cancer Deaths. 2019. http://ghdx.healthdata.org/gbdresults-tool (accessed Dec 15, 2023)
12 van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, Tjan-Heijnen VCG, Janssen DJA. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage 2016; 51: 1070–90.e9.
13 Kim YC, Ahn JS, Calimag MM, et al. Current practices in cancer pain management in Asia: a survey of patients and physicians across 10 countries. Cancer Med 2015; 4: 1196–204. 14 Li Z, Aninditha T, Griene B, et al. Burden of cancer pain in developing countries: a narrative literature review. Clinicoecon Outcomes Res 2018; 10: 675–91.

15 El Bcheraoui C, Mimche H, Miangotar Y, et al. Burden of disease in francophone Africa, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Glob Health 2020; 8: e341–51. 16 Kurth AE, Cherutich P, Conover R, Chhun N, Bruce RD, Lambdin BH. The opioid epidemic in Africa and its impact. Curr Addict Rep 2018; 5: 428–53.

17 Edan C, Yao AJJ, Hessissen L, et al. Integrating a palliative approach into the healthcare provided by the French-African Pediatric Oncology Group's pilot units. Insights from a 3-year training program. Arch Pediatr 2021; 28: 166–72. 18 United Nations. Single Convention on Narcotic Drugs, 1961. https://www.unodc.org/pdf/convention 1961 en.pdf (accessed Feb 25, 2024). 9 World Bank. The world by income and region. 2023. https:// datatopics.worldbank.org/world-development-indicators/the-worldby-income-and-region.html (accessed Dec 3, 2023 20 The Global Cancer Observatory. All cancers: Globocan 2020, 2020. https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancersfact-sheet.pdf (accessed Dec 11, 2023). Gershman B, Rivera D. Measuring regional ethnolinguistic diversity in sub-Saharan Africa: surveys vs. GIS. World Bank Econ Rev 2019; 34: \$40–45.
Cleary J, Powell RA, Munene G, et al. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Africa: a report from the Global Opioid Policy Initiative (GOPI). Ann Oncol 2013; 24: xi14–23.
Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. CA Cancer J Clin 2018; 68: 182–96. 4 South African National Department of Health. The National Department of Health. The National Department of Health. South Africa: Essential Drugs Programme, 2020. https://knowledgehub.health.gov.za/content/standardtreatment-guidelines-and-essential-medicines-list (accessed Feb 22, 2024 nternational Narcotics Control Board, Availability of internationally controlled drugs; ensuring adequate access for medical and scientific purposes, 2015, https://www.incb.org/documents/ Publications/AnnualReports/AR2015/English/Supplement-AR15 availability English.pdf (accessed

Boumelha J. Tackling cancer the Tunisian way. Cancer World, 2007. https://archive.cancerworld.net/wp-content/uploads/2017/07/1701_ CW16_34-39_masterpieceOK.pdf (accessed Feb 10, 2024).

28 Hadjiat Y, Perrot S. Cancer pain management in French-speaking African countries: assessment of the current situation and research into factors limiting treatment and access to analgesic drugs. Front Public Health 2022; 10: 846042. 29 Grant L, Leng M, Fallon M. Pain workshop ESMO: Africa (response). ESMO Open 2020; 5: e000833. 30 Fisch MJ. Palliative care education in Ghana: reflections on teaching in West Africa. J Support Oncol 2011; 9: 134–35.

27 The Global Cancer Observatory. Cancer Tomorrow. 2023. https://gco.iarc.fr/tomorrow/en (accessed Dec 11, 2023).

Hadjiat Y, Toufiq J, Ntizimira C, Arendt-Nielsen L, Burucoa B, Treillet E, Authier N, Perrot S. Analysis of opioid analgesics consumption in Africa: a longitudinal study from a 20-year continental perspective. Lancet Glob Health. 2024 Jul;12(7):e1120-e1128. doi: 10.1016/S2214-109X(24)00146-3. PMID: 38876759.