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FEATURE ARTICLE:

Quality Evaluation of Selected Emtricitabine/Tenofovir Disoproxil Fumarate 200/300mg Fixed Dose Combination Tablets Registered in Kenya

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The Pharmaceutical Society of Kenya (PSK) is a representative organization that was formed enabling Pharmacists' to employ their professional expertise in the care of patients.

Established in 1964, PSK has its roots in the Pharmaceutical Society of East Africa, which was registered in 1950. Since its formation, PSK continues to promote a common standard for professional conduct and code of ethics for its members, as well as advocate for the welfare of Pharmacists.

EDITORIAL

READING, WRITING, AND PUBLISHING IN PHARMACY PRACTICE: WHY BOTHER?

Prof. Apollo O. Maima, PhD, MPSK
Editor-in-Chief and Chair of the Editorial Board, Pharmaceutical Journal of Kenya

The processes of reading, writing, and publishing play a crucial role in pharmacy practice and research, serving as foundational elements for evidence-based healthcare. Proficient writing ensures the clear communication of clinical guidelines to patients and highlights the importance of effectively sharing information within the field. Pharmacy education prioritizes knowledge literacy, which requires practitioners to grasp scientific principles thoroughly. Engaging in academic pursuits fosters lifelong learning, bridging the gap between theoretical scientific knowledge and its practical implications, thereby aligning professional expertise with public health medication policies.

Pharmacists must employ specialized strategies within their academic endeavours to identify challenges and develop hypotheses. The reading process synthesizes diverse sources of information, while the writing component focuses on producing knowledge suitable for publication. Achieving intellectual autonomy and adhering to best practices are crucial elements. Commitment to patient care necessitates ongoing engagement with literature and the integration of knowledge. The ambiguities surrounding drug therapy underscore the importance of evidence-based data, which combines clinical acumen, patient values, and research to inform decision-making effectively.

Thorough documentation of the rationale behind clinical decisions, while simultaneously addressing patient viewpoints, is of paramount importance. Mastery in reading, writing, and publishing equips pharmacists to fulfil their societal obligations, as these skills are indispensable tools that reinforce their commitment to patient care and engagement with the healthcare system. Reading serves as the foundation for effective practice, ongoing education, and informed clinical decision-making, connecting practitioners to the current standards and reinforcing their knowledge base.

Continuous professional education and extensive reading are in accordance with licensing criteria, fostering elevated standards. Regular duties require adept documentation that not only ensures patient safety but also demonstrates professional integrity. Effective written communication is essential for interactions with regulatory bodies, thereby establishing credibility within pharmaceutical practices. High-quality clinical documentation standardizes terminology, guaranteeing both clarity and adherence to regulations.

Effective writing underpins pharmacists' accountability and legitimacy, and contributions to peer-reviewed journals are critical for disseminating knowledge and advocating for advancements in care. Pharmacists' publications significantly enhance practice and patient outcomes, aligning with the Health Professions Accord. Evidence-based information and patient data are vital for clinical decisions, ensuring adherence to national guidelines and quality care. Systematic safety reporting is essential for public health. Educational institutions emphasize pharmacy knowledge and literacy skills. Mentorship and interprofessional collaboration are key for professional development and effective knowledge transfer. Emphasizing the importance of literacy in reading, writing, and publishing enables pharmacists to advance their practice in response to the changing demands of the healthcare environment.

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Reshaping Kenya's Pharmacy Future (*A letter to Kenyan Pharmacists*)

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A new mother, racing between infant feedings and sleepless nights, taps a pharmacy app to request an urgent prescription—less than two hours later, a rider arrives at her door with the medication, sparing her a day lost to traffic jams. Across the city, a corporate lawyer orders a prescription refill during a coffee break; it arrives at her office before her next client call. These are not miracles of convenience—they are the new reality of Kenyan pharmacy, where digital platforms dissolve barriers to care and pharmacists evolve into architects of health access.

Given Kenya's medication access and distribution challenges, documented in Toroitich et al. [1], online pharmacy services serve as an efficient tool for addressing this long-standing problem for healthcare in the country. Despite the increase in momentum for the utilization of digital pharmacies, a crucial question that arises is: "What role will Pharmacists play in the digital transformation of pharmaceutical service delivery?"

In this article, the potential of online pharmacies, consequential challenges faced by pharmacists and the need for a central role for Pharmacists in the digital transformation of pharmacy services, are explored.

Why Online Pharmacies Matter: Growth and Opportunities

Transformation in the procurement process for medication, due to online pharmacy services, can be seen in the optimization of delivery for efficiency, an increase in healthcare services accessibility and implementation of competitive pricing structures. Research demonstrates that digital platforms achieve cost efficiencies through operational optimization and reduced overhead expenses, while market competition facilitates consumer-favourable pricing [2]. Emerging markets are areas of potential growth, as noted in Singh and Kumar for the case of India and its accelerated expansion in digital pharmacies [3]. With advances in digital infrastructure and systems, Kenya is well-positioned to pursue similar developments in digital pharmacies as India. Projections for investment opportunities into e-commerce for Kenya show that revenues are expected to reach US$922.10 million by 2025 end of year, with an expected annual growth rate (CAGR 2025-2029) of 4.20%; which will result in a projected market volume of US$1,087.00 million by 2029 [4.] With an industry-wide projected growth for eCommerce, digital pharmacies represent a viable investment option in Kenya, presently and into the future.

The COVID-19 Pandemic represented a shift in e-commerce. Nyambega et al. explain that a shift in consumer behavior was noted during the pandemic, which favored the utilization of e-commerce there-after [5]. Considering this post-pandemic shift in consumer behavior and the high penetration of internet and smartphone use, noted in Kharono et al. Kenya is anticipated to present substantial growth opportunities for online pharmacy services [6].

Building Digital Trust: The Consumer Perspective

Trust establishment has, over time, remained fundamental to the success of any business. In the case of digital pharmacies, consumers require assurance regarding medication authenticity, data security protocols, and comprehensive healthcare service delivery. Pharmaceutical professionals play a central role in addressing these concerns. They facilitate consumer understanding of reliable digital pharmacy identification through patient education and platform functionality explanation. Pharmaceutical professionals also provide guidance in distinguishing legitimate platforms from unauthorized operations [7.] As a result, the role played by pharmaceutical professionals enhances consumer confidence in digital pharmaceutical services. Additionally, professional involvement in quality standard implementation encourages broader adoption of digital pharmacy services, which can potentially encourage industry expansion across Kenya.

How Local Pharmacies Can Adapt

Traditional pharmacies maintain distinct advantages over purely digital platforms, including direct patient consultation capabilities and immediate medication accessibility. By integrating digital services with these core strengths, conventional pharmacies can enhance customer experience; in a hybrid service structure. Implementation strategies might include online prescription refill systems with in-store collection options or targeted home delivery services. From a financial perspective, digital pharmacy performance metrics require detailed evaluation methodologies compared to traditional operations. Key performance indicators, such as

customer retention rates, delivery cost optimization and digital marketing effectiveness, provide crucial insights for business strategy development.

Leading the Change: How Pharmacists Shape the Digital Future

The increasing adoption of digital health services necessitates the integration of pharmaceutical expertise with technological advancement. This integration requires continuous professional development, regulatory framework contribution, and prioritization of patient-centered care in digital platforms. However, given that the products and services are primarily pharmaceutical based, pharmacists need to be at the forefront of the digital future of medication access and distribution.

Immediate professional engagement is necessary to maintain industry control of online pharmacy services. Delay in engagement may create a gap that would be filled by business and technology professionals who might not prioritize pharmaceutical care requirements, with likely tradeoffs in favor of commercial objectives, potentially compromising professional standards and patient outcomes.

Professional pharmaceutical services extend beyond medication dispensing to encompass patient education, drug interaction monitoring and safety protocol maintenance. These competencies become increasingly vital in digital environments where patients require expert guidance. On the part of pharmaceutical professionals, the integration would involve upskilling in terms of gaining skills and knowledge in digital marketing in healthcare. Professional integration in digital platforms thus enables the development of a comprehensive healthcare system that optimizes both traditional and digital service delivery methods.

Moving Forward Together

The profession's continued relevance and impact are dependent upon the capacity to adapt, innovate and continuous collaborative engagement. To secure the future of the pharmacy practice in Kenya, immediate strategic action and professional leadership is required.

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Leveraging Pharmacoepidemiology and Pharmacovigilance (real world) Data to Monitor Antimicrobial Resistance and Misuse: A Narrative Review

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Abstract

Antimicrobial resistance (AMR) is a worldwide challenge requiring urgent multidisciplinary solutions. Pharmacoepidemiology (P.E.) research and real-world data, including patient clinical encounter data, pharmacovigilance (P.V.) data, drug utilisation data, drug safety data, and post-marketing surveillance (PMS) data, could enhance existing antimicrobial stewardship strategies.

This article highlights how the P.E. and P.V. databases can provide data and information on suspected antimicrobial resistance and inappropriate use of antimicrobials and offer solutions for AMR.

The literature about Pharmacoepidemiology, antimicrobial resistance, and antimicrobial stewardship was obtained by searching through various databases such as Google Scholar, PubMed, and Cochrane Library. This review identified and sorted the literature on Pharmacoepidemiology, Pharmacovigilance, antimicrobial resistance, and antimicrobial stewardship.

Information abstraction: information about P.E., P.V., AMR, and AMS was obtained by targeting the comparability and utility of AMR.

Pharmacoepidemiology and P.V. databases provide valuable information about the potential misuse of medicines, including antimicrobials. The antimicrobial stewardship (AMS) program is an efficient strategy for P.E. and P.V. to rationalise antimicrobial utilisation. Studies have identified MedDRA preferred terms (PTs) applicable to produce data on antimicrobial ineffectiveness, resistance, off-label use, and medication errors. If linked to antibiotics, ADR reports can help develop policies that guide appropriate antibiotic use and, therefore, contribute to the fight against antimicrobial resistance.

Pharmacoepidemiology and Pharmacovigilance systems can directly assist and inform policies and medicines regulatory processes when developing a global or a National Action Plan on Antimicrobial resistance.

Key Words: *Antimicrobial resistance, Pharmacoepidemiology, real-world data/evidence, and Pharmacovigilance.*

Introduction

Antimicrobial Resistance and Antimicrobial Stewardship

Antimicrobials are broad-spectrum medicines that treat and prevent human, animal, and plant infections [1]. These medicines kill or inhibit the proliferation of microbes responsible for infections. Because of their reputation, antibiotics tend to be misused, leading to health-related problems like numerous adverse drug reactions (ADRs) related to antibiotics that challenge healthcare delivery [3,4]. With prolonged exposure to suboptimal antibiotic doses, antimicrobial resistance (AMR) gradually arises as the bacteria acquire the ability to hinder the antimicrobial action of the formerly effective drugs [2]. The resistant organisms successively cause superinfections, which are difficult to treat with broad-spectrum antibiotics [5]. AMR and the rising healthcare costs due to antibiotic overuse require unique strategies for effective control [6].

Antimicrobial resistance is a universal challenge that impacts people of all ages. If effective antibiotics were available, it could save many lives [1]. It is estimated that 5.7 million fatalities occur yearly from curable infectious diseases, primarily in low—and middle-income countries (LMICs). Concurrently, about 700,000 deaths occur annually globally due to antibiotic resistance, and if no action is taken, the number may rise to over 10 million in 2050 [2].

The antimicrobial stewardship (AMS) program consists of interventions aimed at targeted patient outcomes. Its primary goals include controlling antibiotic-related adverse effects, minimising antibiotic resistance, reducing the incidence of superinfections, and lowering the overall therapy cost [7]. The AMS program emphasises the selection of antimicrobials based on a culture sensitivity test (CST), the optimum duration of therapy, and the choice of an oral route over a parenteral route of antimicrobial administration [8-10]. Therefore, AMS involves promoting the responsible use of antimicrobials to minimise the development of resistance.

Despite efforts to roll out AMS in most countries, a globally coordinated strategy still needs to be developed to curb increasing resistance. Limited AMS involvement challenges

global coordination at the primary healthcare level, with pharmacies issuing antimicrobials without a valid prescription and overusing antimicrobials in non-human sectors [11]. Multiple types of AMS programs, categorised as persuasive, restrictive and structural, have been established across various countries at different levels of healthcare delivery, involving a diverse array of stakeholders such as clinicians, pharmacists, nurses, veterinarians, administrators, and healthcare facilities [12,13].

Conserving antibiotic effectiveness while ensuring universal access is central to public health challenges. Policies promoting ease of access must be aligned with strong measures to minimise inappropriate use that would lead to increased resistance [12, 13]. To enhance universal accessibility to antibiotics while safeguarding appropriate use, the World Health Organization (WHO) established a classification system in 2017 for antimicrobials on its Essential Medicines List (EML). This system classified antimicrobials into three groups: "Access," "Watch," and "Reserve" (AWaRe). The classification is based on factors such as the drug indication, its availability, and the level of awareness regarding its application [14]. Governments and other health organisations were urged to implement the AWaRe tool. [14]

As the world takes various measures to combat the growing threat of antibiotic resistance, P.E. data and P.V. data can play a crucial role in developing comprehensive multidisciplinary approaches for AMR monitoring and early warning systems. The AWaRe categorization is a valuable tool for monitoring efforts aimed at specific antibiotics.

Pharmacoepidemiology

Pharmacoepidemiology involves studies on drug use effects at the population level and the risks associated with these uses. P.E. is concerned with the variance of drug effects between individuals in a population and between populations. P.E. is an emerging speciality that deals with medication use in a large population, identifying and quantifying adverse drug reactions, and quantifying the risk or benefit of medication for a particular disease or condition [21].

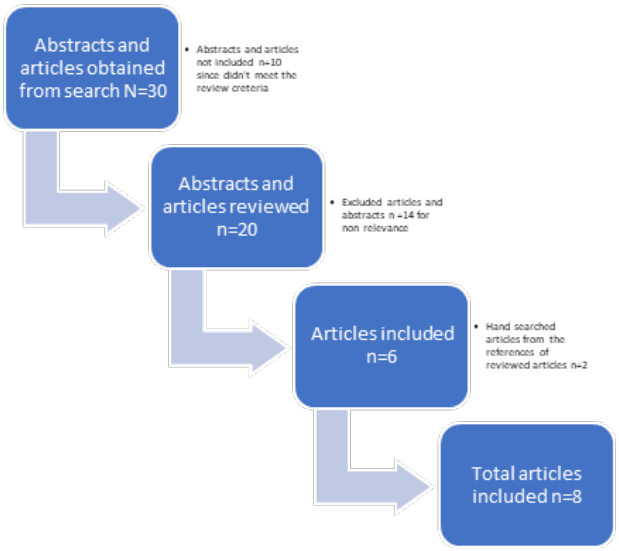
Pharmacovigilance encompasses the scientific and regulatory efforts to detect, assess, understand, and prevent adverse effects or other drug-related problems. Adverse event reports are the primary tool for safety signal detection [21-22]. Pharmacovigilance, also known as drug safety surveillance, focuses on the 'timely detection' of 'novel' adverse drug reactions (ADRs) characterised by their unique 'clinical nature, severity, and frequency [21]. Post-marketing surveillance (PMS) involves monitoring marketed medicines for ADRs after clinical trials [22].

Methodology

This review was conducted through a literature search on Pharmacoepidemiology, antimicrobial resistance, and antimicrobial stewardship using various databases, such as Cochrane Library, Google Scholar, and PubMed, between June 2023 and December 2024. The reviewed articles' references were explored to identify significant studies on Pharmacoepidemiology and antimicrobial resistance.

The search was conducted using a specific term ("Pharmaco-epidemiology" OR "pharmacovigilance" OR "real world data" OR" real world evidence") AND ("antimicrobial" OR "antibiotics" OR "anti-bacterial agents") AND ("antimicrobial resistance" OR "lack of effectiveness" OR "antibiotic resistance" OR "drug ineffective" OR "drug misuse" OR "off-label use"). The search yielded 30 articles, but only 8 English titles were selected for review.

Study selection: All abstracts, titles, and articles were reviewed, and all non-English articles with no translation and articles unrelated to Pharmacoepidemiology and antimicrobial resistance were excluded. This review primarily focused on studies related to AMR and the AMS programs and P.E. studies of various study designs, namely, case-control studies (CCT), randomised controlled trials (RCT), and cohort studies, to assess these programs. The figure below shows the article selection process.



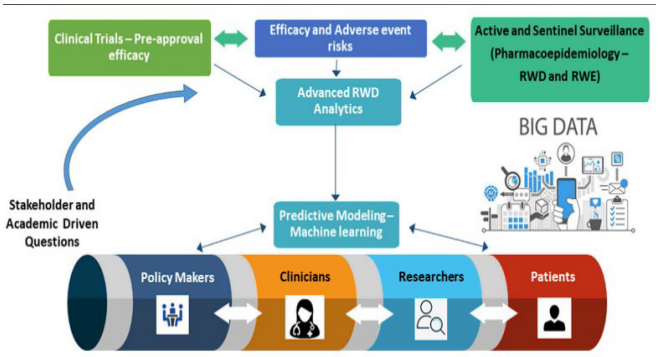
Information abstraction: Information about P.E., P.V., AMR, and AMS was obtained and summarised by targeting the comparability and utility of AMR and P.E. Information synthesis: The information collected after reviewing the articles covering the scope of P.E., P.V., and drug safety and their contribution to AMR and AMS was structured and interpreted based on the contribution level.

Role of Pharmacoepidemiology and Pharmacovigilance in Antimicrobial Stewardship Programs

PE and PV data and clinical bedside use

Pharmacoepidemiology and Pharmacovigilance data can highlight use-related issues, giving prescribers a bigger picture and helping them make choices during each consultation. Researchers can share P.E. and P.V. database reports on off-label drug use or usage in contraindicated indications with units in charge of national policies on antimicrobial use to promptly inform the policy-making

{figure below. Borrowed from Bérard A (2021). }[20, 23]



Real-world data (RWD) or big data obtained from the PE studies can aid in making clinical decisions at the bedside. This data can be integrated into HMIS, including the AfyaKe, currently used in public hospitals in Kenya to facilitate clinician access, or in computer applications like AI to aid decision-making. [24 and 25]

Artificial intelligence (AI) might seem like a science fiction concept, but modern algorithms affect our everyday lives. For instance, online advertisements that appear to be tailored to individual preferences result from AI predicting purchasing behaviour through data analytics by analysing one's history and patterns. This same technology can help to choose the most suitable antibiotic for a specific patient. By applying similar methods, we can analyse extensive data from electronic medical records to develop predictive models that enhance the accuracy and reliability of antibiotic prescriptions, moving beyond the current method of 'educated guess' or empirical approach.[14,15, and 20]

PE and PV data and antimicrobial utilisation

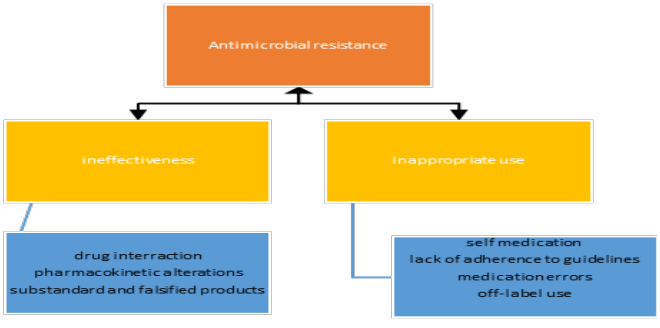
The PE and P.V. data can help identify adverse drug reaction (ADR) reports related to antibiotics on the Reserve and Watch list; this is particularly relevant from an AMR standpoint. [20] The ADR reports provide insights into the off-label or excessive use of Watch and Reserve antibiotics, considering their indications and available formulations. [1,6]

Medical dictionaries also categorise adverse events with terminology that highlights their usage-related aspects, besides standard adverse reaction terms such as nausea, vomiting, diarrhoea, hypersensitivity, and headache. These terms encompass occurrences like "absence of the expected therapeutic effect," "ineffectiveness," "misuse," "usage beyond indications," and even "suspected antibiotic resistance." These classifications are found in the Medical Dictionary for Regulatory Activities (MedDRA) [1,20,23]. These terminologies are standardised internationally and widely applied globally in health information technology and pharmacovigilance (PV) databases [23]. Locating reports with such terms in PV databases could serve as an indicator of potential misuse or concerns about resistance when specific detection methods for these concerns are lacking [20,23].

Research has shown that it is possible to detect treatment failures caused by antimicrobial resistance (AMR) in adverse drug reaction (ADR) reports in VigiBase. This is achieved by identifying groups of terms associated with the lack of an expected therapeutic effect. Notably, these terms were reported as the 9th most commonly reported ADR [20, 21]. Studies have shown how PV data could significantly contribute to monitoring AMR by associating suspected adverse event reports with antibiotics used in treating carbapenemase-producing Klebsiella pneumoniae (KPC) infections across three varying databases in two countries with differing KPC prevalence (Italy with high prevalence(2% to 9%) and the United Kingdom with low prevalence at 3.8%), utilising data on culture isolates given by the European Centre for Disease Prevention and Control. The established positive correlations, Italy ($p < 0.01$; $p = 0.005$) and UK ($p = 0.032$; $p= 0.013$), indicated an overall increase in adverse events, explicitly highlighting terms associated with AMR: "drug ineffective," "drug resistance," "pathogen resistance," "off-label use," and "product use issues." The findings also pointed to serious adverse events associated with KPC outbreaks in both countries, showcasing the potential for earlier identification of AMR outbreaks by tracking the trends of adverse event notifications related to antibiotics [20,23].

Pharmacovigilance aims to generate alerts regarding suspected adverse events. When analysing multiple such suspicions linked to the same medication within a specific area, these related reports, which may use different terms to describe similar types of adverse events, form a cluster. This clustering triggers an alert or signal. Thus, pharmacovigilance is vital for investigating these concerns and identifying the root causes, which may include either resistance or improper usage.

The figure below depicts a model that showcases the connections between factors affecting real-world antibiotic use and their correlation with AMR, which can be identified in PE and PV studies. [20,21].



PE and PV data to help identify the inappropriate use of antibiotics and thus prevent antimicrobial resistance

Pharmacoepidemiology offers methods and tools to AMS programs that assist in monitoring suspected resistance or inappropriate use of antimicrobials, aiding in controlling the rising antimicrobial resistance. Drug utilisation studies that

inform the drug use patterns in a system can tell or predict AMR and help point out the weak links in the AMS programs. [2]

Disproportionally more considerable reporting on antimicrobial treatment failure can indicate two major public health issues: antimicrobial resistance and medicines of poor quality [15]. A public health threat arises where the latter triggers the onset of the former. Detection of observed-to-expected ratios of reported clusters of adverse events can enable identifying resistance spread patterns in the respective area.[2,15.20]

Pharmacoepidemiology studies can assess the use of specific medications in various contexts, offer insights into the human behavioural and epidemiological changes populations experience, and indirectly assess the risks and benefits [16,20]. Reports of spontaneous data are essential for identifying safety signals associated with the use of medicines after marketing approval, reflecting their use in real-world scenarios. [20].

A pharmacovigilance study has identified 17 MedDRA preferred terms (P.T.s) relevant for gathering data on antimicrobial ineffectiveness, resistance, unapproved use, and medication errors (i.e. RIOLE framework can aid in analysing and managing adverse drug reactions and other safety issues associated with antimicrobials).[20]. If associated with antimicrobials, ADR reports can assist the development of policies to offer guidance on the appropriate use of antibiotics and contribute to the fight against antimicrobial resistance [20].

The inappropriate use of antibiotics (ABs) is a major cause of antimicrobial resistance (AMR) in Africa, where infectious diseases are prevalent. High consumption and misuse of antimicrobials are linked to poor adherence to prescribing guidelines, prolonged prophylaxis, and the use of multiple antimicrobials in the Watch group.

Case study

A study by Ballon et al. in the French Pharmacovigilance Database (2010–2019) found that adverse events (AEs) involving anti-infective drugs were more common among pregnant women (8.1%) compared to nonpregnant women (1.6%). These AEs included "lesions, poisoning, and surgical complications" often related to medication errors. [1,20, 22]

Case study

Research in Russia found that medication errors were the primary risk factor for increasing microbial resistance. These errors included using antimicrobials without proper indications or for the wrong indications, incorrect dosages and regimens, and administering contraindicated drugs associated with using beta-lactams. [18,21] Prompt reporting and accurate coding of these errors in a spontaneous ADR reporting database can advise policy on the appropriate use of antibacterials. Several studies observed treatment failure as a reportable event [22]. Hence, it is important to define failure properly if pharmacovigilance systems are systematically used to collect data on failure.

Case study

In a review by Ren et al., cephalosporins safety was examined in Chinese pharmacovigilance (PV) databases (2009–2010), revealing 1337 adverse events (AEs). The findings showed that misuse, including inappropriate dosing regimens, occurred in 93% of patients (n = 1243), while overuse was noted in 18% (n = 249), with children being more significantly affected [19,20]. These studies highlight how reported adverse event terms can help identify antibiotic overuse and misuse.

Case study

In India, a study on multidrug resistance to ceftriaxone/tazobactam and amikacin revealed inappropriate usage, primarily for empirical prophylaxis, with susceptibility tests only performed after initial treatment failure. This led to resistance and the need for substitutes like meropenem (Watch) or linezolid (Reserve).

PE and PV data to help identify the ineffectiveness of antibiotics and thus prevent antimicrobial resistance

Healthcare professionals globally play an essential role in collecting and submitting safety data to regulatory authorities. The Guideline on Good Pharmacovigilance Practices (GVP) Module V (EMA) mandates addressing and treating unwanted clinical outcomes for which enough evidence indicates that the medicinal product caused them, as adverse drug reactions (ADRs). [21,22] Thus, AMR and antimicrobial ineffectiveness are undesirable clinical outcomes. Considerations should be made to use AMR-suitable MedDRA terms when capturing data to appraise risk management plans. The GVP states that ADR reports may come from various sources, like spontaneous reports, and can be associated with non-approved use and medication errors. If the medicinal product is an antibacterial, regulatory authorities should evaluate the risks related to non-approved use and consider its use in the context of antimicrobial stewardship.

Using PE tools and methods such as epidemiologic and statistical models to assess the benefits and risks of antibiotics in particular patients or groups of patients with unique characteristics can help individualise antimicrobial therapy and thus reduce its misuse and mitigate other risks associated with antimicrobial use. Such tools and methods include periodic reports (PEBRER, PSUR, and RMPs), epidemiological models like multicriteria decision analysis (MCDA), Q-TWIST, and Co-joint analysis. The periodic benefit-risk evaluation report (PBRER) can track antimicrobial resistance (AMR) trends and pinpoint factors contributing to its development and spread, such as increased hospitalisations and antibiotic treatments during the COVID-19 pandemic. The PBRER can also guide regulatory actions and public health interventions to prevent and manage AMR [17,21,22].

There are MedDRA terms in Pharmacovigilance databases that denote an absence of effect, like “drug ineffective,” “treatment failure,” “decreased drug efficacy,” and “therapy

nonresponder" [20]. It is essential to monitor signs related to these events while investigating their causes. Additionally, adverse events related to ineffectiveness may also indicate potential resistance to the involved antimicrobial [20].

Case study

An analysis of VigiBase data from 1968 to 2018 covering 1,170,751 antimicrobial-related adverse events (AEs) identified 15,250 (1.3%) reports involving 17 MedDRA PTs relevant to antimicrobial resistance (AMR). The six medicines most frequently reported and accounted for 38% of the alerts (n = 5806) were: Amoxicillin (n = 873; 5.7%; Access), Cephalothin (n = 151; 1%; Access), Ciprofloxacin (n = 1748; 11.5%; Watch), Clarithromycin (n = 991; 6.5%; Watch), Levofloxacin (n = 1342; 8.8%; Watch), and Daptomycin (n = 701; 4.6%; Reserve)

The common terms reported in these notifications included"drug ineffective" (n = 6959; 45.6%), "off-label use" (n = 1455; 9.5%), and "pathogen resistance" (n = 1327; 9.0%) [19,20, and 21].

Case study

A review of the EU pharmacovigilance (PV) databases (Eudravigilance updated 2022) examined the link between MedDRA terms for"drug resistance"and"drug ineffectiveness" and 3 antimicrobials often used for seriously ill patients: meropenem (n = 8864; Watch), colistin (n = 983; Reserve), and linezolid (n = 13,381; Reserve). Colistin had higher reports of "drug resistance" (8.4%) compared to meropenem (3.6%) and linezolid (2.4%). Colistin was most frequently associated with "drug ineffectiveness" (10.1%), followed by meropenem (9.5%) and linezolid (4.2%). [19,20]

Deaths linked to suspected bacterial resistance occurred in 20% of meropenem cases, 24% of colistin cases, and 6% of linezolid cases. For "drug ineffective" cases, death was observed in 28% of meropenem, 35% of colistin, and 19% of linezolid cases. The study implied that colistin was more likely to be linked with resistance and inefficacy reports compared to other antimicrobials, except ceftazidime/avibactam [19].

Case study

A study on tigecycline-associated adverse drug events reported to the FDA Adverse Event Reporting System from 2004 to 2009 observed 1182 occurrences, with "drug is ineffective" being one of the most frequently reported events (63 cases; 5.33%) and "pathogen resistance" also notable (22 cases; 1.86%) [19, 20]. Another study on the same database from 2015 to 2018 identified 5899 notifications linked to carbapenems, with "drug ineffective" again being the most frequent event (620 cases; 10.51%) [19, 20].

These studies emphasize that spontaneous reports of suspected adverse drug reactions (ADRs) can indicate both drug ineffectiveness and the risk of potential antimicrobial resistance. Such data can be analysed to comprehend the root causes of the reported adverse events.

Discussion on future directions

Pharmacoepidemiology and Pharmacovigilance systems can directly assist and inform policies and medicines regulatory processes when developing a global or National Action Plan on AMR. Hence, they can catalyse and strengthen systemic and cultural change in managing and using antibiotics to ensure their effectiveness and longevity for future generations.

Enhancing the role of pharmacovigilance involves promoting current tools and methods and training reporters on observed or suspected effects. Creating awareness of AMR-suitable MedDRA terms and describing their relevance to antimicrobial resistance surveillance would increase prescribers' and patients' submissions of similar reports.

Pharmacovigilance centres at the county or national level should actively advocate these AMR-suitable PTs and welcome individuals to gather and submit this information to the appropriate agencies. Active involvement in this process has several advantages: (1) more spontaneous reports will be sent to the PV centres, and its effort will be more noticeable and valued by other health key players, and (2) prompt detection of suspected AMR and thus fast response to control and prevent it. Integrating pharmacovigilance into AMS could foster collaboration among various scientific disciplines addressing antimicrobial resistance from previously isolated viewpoints. Using the existing methods and tools to solve the AMR challenges will also allow P.E. and P.V. to evolve and develop further. Moreover, countries will recognise the increased importance of investing in their pharmacovigilance systems. As technological advances in pharmacovigilance develop, traditional post-marketing drug safety monitoring methods can also be effective surveillance strategies for AMS programs.

Conclusion

This review showed that real-world data comprising P.E. and P.V. data can generate evidence-based medicine to assist in AMS. When information/evidence to support the use of medicine is sought, they critically appraise the information/evidence and integrate the appraised evidence with the clinician's clinical expertise and patient preferences. Then, they are involved in evaluating the clinical outcome. Pharmacoepidemiology and P.V. are beneficial in generating the database on the ADRs associated with the misuse of antimicrobial agents.

Pharmacoepidemiology (PE) and pharmacovigilance (PV) studies can enhance antimicrobial use by supplementing the known safety profiles of antimicrobials. Pharmacoepidemiology and PV can assist in picking out both antimicrobial ineffectiveness and inappropriate use. These tools, widely established in several countries, can guide AMS and other drug policies, alerting authorities and healthcare providers to potential antibiotic resistance.

Incorporating these strategies as signals of misuse and resistance in AMS can have significant impacts. Understanding the causality of these events and promoting specific alerts can greatly benefit stewardship programs. This review has demonstrated how well-established public health tools can support AMS activities and address resistance issues. Enhancing pharmacovigilance systems and promoting the reporting of adverse events related to antimicrobial resistance (AMR) is vital for monitoring antibiotic usage and improving AMR-related policies and stewardship programs.

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Quality Evaluation of Selected Emtricitabine/ Tenofovir Disoproxil Fumarate 200/300mg Fixed Dose Combination Tablets Registered in Kenya

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Abstract

Background: Emtricitabine and Tenofovir Disoproxil Fumarate fixed-dose combination tablets are key in the management and prophylaxis of Human Immunodeficiency Virus. However, recent product recalls indicating quality issues among antiretrovirals in Kenya highlight the importance of routine post-marketing surveillance.

Objective: The study aimed to evaluate the quality of an innovator brand batch and five selected batches of generic emtricitabine/tenofovir disoproxil fumarate (200mg/ 300mg) fixed-dose combination tablets sampled from different parts of Kenya.

Methods: The quality evaluation was carried out using compendial tests; uniformity of weight, hardness, dimensions, disintegration, dissolution, identification, and assay as per The International Pharmacopeia, United States Pharmacopeia, and British Pharmacopeia guidelines.

Results: The results of the innovator brand, Truvada®, were compared to those of five batches of the generic brand Mylan®, with reference to official compendial specifications. All the brands complied with the compendial specifications for uniformity of weight, disintegration, hardness, identification, dissolution, and assay. The principal peaks for both brands had retention times corresponding to those of the respective standard solution, thus confirming the identity of the tablets. After 30 minutes of dissolution, all the tablets from the innovator and generic batches released contents of more than 80% for both. All the brands had a percentage content of more than the minimum 90% of the label claim of both emtricitabine and tenofovir disoproxil, and therefore satisfactory for the assay test.

Conclusion: The sampled batches of the innovator brand and generic brand of emtricitabine/tenofovir disoproxil fumarate combination tablets met the quality standards as outlined in the various compendia used. They can therefore be considered safe and efficacious.

Keywords: *Quality evaluation, Emtricitabine, Tenofovir Disoproxil Fumarate, Generic*

Introduction

Human Immunodeficiency Virus (HIV) remains a global public health concern, with an approximate 40 million people living with HIV by 2024, 76% of whom are on treatment. The disease has led to about 40.4 million deaths worldwide, with sub-Saharan Africa, particularly Kenya, having a high burden(1). Kenya has around 1.5 million people living with HIV and an annual mortality of about 25,000 (2). HIV is a retrovirus that weakens the immune system by targeting Cluster Differentiation-4 (CD4) cells. Although there is no cure for HIV, Antiretroviral Therapy (ART) is the standard treatment to block the virus's replication.

Tenofovir disoproxil fumarate (TDF) is a cornerstone of ART, used in first and second-line treatments, in prophylaxis, and in prevention of mother-to-child transmission of HIV. The drug was first approved by the FDA in 2001 for HIV management and later for Hepatitis B Virus (HBV) in 2008. Emtricitabine, approved for HIV treatment in 2003, is also used for HBV, although it is not FDA-approved for this purpose. In 2012, a fixed-dose combination of Emtricitabine and Tenofovir disoproxil fumarate (Truvada®) was approved for both prevention and treatment of HIV(3). In Kenya, Truvada® was approved for prophylactic use by the Pharmacy and Poisons Board in 2015, and thereafter, generic versions have been approved based on bioequivalence data.

Drug quality is crucial for effective disease management and is defined as the totality of product features that meet affirmed and implied needs. Quality control is the sum of all procedures that ensure the identity and purity of a product, thus forming an essential part of good manufacturing practices. Quality evaluation of pharmaceutical products includes physical, physiological, and chemical tests such as visual inspection, friability, disintegration, hardness, thickness, uniformity of weight, and drug content assays.

The World Health Organization (WHO) estimates that 10.5% of medicines, including antiretrovirals, globally are of poor quality (4). These poor-quality medicines are classified either as substandard or falsified drugs. Substandard drugs contain the right active ingredient but fail to meet quality specifications, while falsified drugs are misrepresented in identity, content, or source. Poor-quality medicines are more common in low- and middle-income countries due to a lack of access to affordable medicines, supply chain complexity, limited manufacturing and quality control capacity(5). Poor-quality antiretrovirals (ARVs) can lead to multidrug resistance, reducing their effectiveness and increasing

treatment costs. Therefore, it is very critical to conduct regular quality control tests to ascertain the quality, safety, and efficacy of ARV drugs.

In Kenya, several ARV quality issues have been reported. In 2011, falsified batches of Zidolam-N® were found to be discolored and molded during an HIV treatment program activity in Nairobi (6). In 2022, Universal Corporation Limited recalled batches of its fixed-dose combination tenofovir disoproxil fumarate/lamivudine/dolutegravir combination tablets due to discoloration and defective induction seals(7), raising safety concerns and public uproar. While previous studies on ARV quality in Kenya have been conducted, sample sizes have been too small to draw comprehensive conclusions (8–10). Furthermore, the product recall affecting generic tenofovir disoproxil fumarate/lamivudine/dolutegravir combination tablets from Universal Corporation Limited raised concerns about the quality of antiretrovirals and compliance with pharmacopeial standards. Routine post-marketing quality surveillance is critical to ensure quality products are circulating within the market. This study aims to evaluate the quality of emtricitabine/tenofovir disoproxil fumarate combination tablets in Kenya, contributing important insights into the quality of ARVs in the country.

Objectives

Main objective: To determine the quality of the innovator brand (one batch) and a generic brand (five batches) of emtricitabine/tenofovir disoproxil fumarate 200/300mg combination tablets in Kenya.

Specific objectives: To evaluate the quality of the innovator brand (one batch) and a generic brand (five batches) of emtricitabine/tenofovir disoproxil fumarate 200/300mg combination tablets by assessing their weight uniformity, dimensions, hardness, disintegration time, dissolution, and assay.

Methodology

Research Location and Design: The research was an experimental study to assess the quality of various brands/batches of emtricitabine/tenofovir disoproxil fumarate combination tablets used in Kenya. Quality evaluation employed physicochemical tests as per the International Pharmacopeia, British Pharmacopeia, and United States Pharmacopeia specifications. The tests were carried out within the Quality Control Laboratory of the Pharmacy and Poisons Board (PPB) in Nairobi, Kenya.

Materials, Reagents and Equipment

Samples: Filmed coated tablets of the innovator brand Truvada® and generic brand Mylan® of the same strength (200mg Emtricitabine/300mg Tenofovir disoproxil fumarate) were sampled for this study (Table 1). One batch of innovator brand Truvada® and five batches of the generic brand Mylan®, each bottle having 30 tablets and a remaining shelf life of at least six months, were obtained from different parts of the country during a countrywide, PPB post-marketing surveillance activity. The Truvada® brand/batch was obtained from Nairobi county, while the Mylan® batches were obtained from Trans-Nzoia, Kisumu, and Bungoma counties. The sampled counties were determined using a web-based Medicines Risk-based surveillance (MedRS) tool, which prioritized regions with high HIV prevalence and relatively risky areas regarding poor quality medicines. Collection sites included public, private, and faith-based hospitals within the selected counties, which were randomly chosen for sampling. After collection from the sites, the samples were coded, packed, and transported to a central PPB samples store in Nairobi, where they were stored at a room temperature of approximately 25°C and 40% - 50% Relative Humidity until they were retrieved for analysis. Before analysis, all samples were retained in their original packages and protected from sunlight.

The study samples were donations originally collected during a national post-marketing surveillance sampling, but not previously analyzed.

Apparatus and Equipment

The equipment and apparatus used included the Mettler Toledo EQBA035 micro-analytical electronic weighing balance (Sotax, Switzerland, SN B928947587) with a sensitivity of ±0.1mg, the DT50, EQDT-019 digital disintegration machine (Sotax, Switzerland) fitted with a thermostat, the Multitest 50, EQMT-022 (MT50 model) electronic hardness, thickness, and width tester (Sotax, Switzerland), the DT Electrolab EDT-018LX Dissolution machine (Sotax, Switzerland), and the Nexera XR model EQLCIII-003 HPLC machine (Shimadzu, Japan SN L20305460034). All equipment used was calibrated and well-maintained.

Reagents: For the standards, tenofovir disoproxil fumarate and emtricitabine United States Pharmacopeia Standards manufactured by Rockville Maryland, with potencies of 99.3% and 99.1% respectively, were used. Potassium dihydrogen phosphate was obtained from Merck, Germany (F2094186005), and Hydrochloric acid, Acetonitrile, and Grade 1 water were all purchased from Finar, India.

Procedures

Macroscopic Evaluation: The tablet's physical properties (color, shape, imprints, and scorelines) of the selected batches were recorded, and the tablets were inspected for any physical defect. The product packaging and labelling were also assessed for visibility of product name, strength of active pharmaceutical ingredient (API), batch number, expiry date, recommended storage conditions, number of tablets, presence of user insert, as well as name and address of the manufacturer.

Uniformity of Weight Test: Twenty tablets from each batch were weighed individually, the average tablet weight calculated, and the percentage deviation of each tablet from the mean weight calculated. The deviation criteria were in line with BP specifications: no more than two tablets should deviate by ±5%, and no more than one tablet should deviate by ±10%.

Measurement of tablet dimensions and hardness: Ten tablets per batch were measured for dimensions and hardness. Tablets were required to meet specified dimensions with no more than ±5% deviation, and a minimal hardness of 40 Newton as per United States Pharmacopeia guidelines.

Disintegration test: Six tablets per batch were tested in the disintegration machine using deionized water at 36°C-38°C. The tablets were considered compliant if they disintegrated within 15 minutes, as specified in the International Pharmacopeia.

Assay: The emtricitabine and tenofovir disoproxil fumarate content was determined using high-performance liquid chromatography (HPLC), following USP monographs. The mobile phase was prepared using potassium dihydrogen phosphate, acetonitrile, and water in the recommended ratio. The sample and standard solutions were prepared by dissolving the drugs and standard in the diluent (acetonitrile and water mixture), within the appropriate concentrations.

Chromatographic Conditions: The HPLC separation was achieved using a C18 column with an Ultraviolet detector set at 280nm wavelength with a flow rate of 1.0 ml per minute at 35°C. The injection volume was set at 20µl and the injector temperature maintained at 6°C using a thermostat oven.

Dissolution Test: The dissolution test was carried out using USP dissolution apparatus 2 with hydrochloric acid in water as medium and the vessels rotated at 50 rotations per minute for 30 minutes at 37°C ±1°C. The samples were filtered and analyzed using HPLC under the same conditions used for the assay.

Data Analysis

Identification: The retention time of the principal peaks of emtricitabine and tenofovir disoproxil fumarate in the sample chromatogram was used to identify the compounds by comparison to those in the chromatogram of the standard preparation.

Assay and Dissolution: The principal peak areas were used to calculate the percentage concentration of the active pharmaceutical ingredients in the samples.

Results

Macroscopic Evaluation: Macroscopic evaluation of any pharmaceutical product forms a crucial step in assessing the quality, elegance, and characteristics of the formulation. These characteristics are key in the identification of the drugs by patients as well as healthcare personnel since they are distinctive and unique. The innovator brand was a light blue caplet-shaped tablet debossed with GILEAD encryption on one side and 701 on the other side. The generic brand was a blue caplet-shaped tablet debossed on one side with M117 encryption and plain on the other side. For both brands, the tablets were packaged in a tightly sealed high-density polyethene (HDPE) bottle with a lid and desiccant inserted inside to absorb moisture. Both primary and secondary packaging in the two brands were well labelled, clearly indicating the product name, strength of APIs, batch number assigned by the manufacturer, expiry date, storage conditions, name and address of the manufacturer. All the containers had 30 shiny film-coated tablets as indicated on the labels (Table 1).

Uniformity of weight: The uniformity of weight test predicts the consistency of the API within a narrow range around the label claim in the dosage units for high-dose tablets. All tablets from the five generic batches and the innovator brand batch complied with the BP specifications for uniformity of weight since no tablet deviated from the average mean weights by more than ±5% as shown in Table 2. This suggests optimal unit operations, such as mixing, granulation, and powder flow, during tablet formulation and a reproducible coating process, hence a uniform tablet weight across the batches.

Tablet Dimensions and Hardness: All the tablets had satisfactory dimensions since none deviated from the expected values by ±5% as shown in Table 2. The tablet hardness is an indication of tablet resistance to fracture during handling, and it also influences other characteristics such as disintegration and dissolution. The innovator brand batch had the highest breaking force of 265N, while the generic brand batch C004 had the lowest resistance of 182N. All the batches had satisfactory results above the minimum USP requirement of 40N as shown in Table 2.

Disintegration: The innovator brand batch had the slowest average disintegration time of 3:24 minutes, while the generic brand batch C001 had the fastest disintegration time of 1:06 minutes. The disintegration time distribution was very narrow, as observed in Table 2. Generally, it is expected that tablet hardness influences the disintegration and, therefore, the corresponding values should be proportional. However, this was not the case as observed in Table 2. Critically, all the tablets complied with the Ph. Int and BP specifications of a disintegration time of less than 15 minutes for film-coated tablets.

Dissolution: Dissolution is a compendial test that measures the concentration of a drug product dissolved in a given medium after a specific time. Hydrochloric acid was used as the dissolution medium to mimic the acidic nature of the gastric environment. It may be expected that tablet hardness impacts dissolution proportionally; however, this was not observed in the study. Notably, variations in other factors, namely the API characteristics, e.g., particle size, solubility, wettability, and morphology, as well as the formulation processes and excipients used, also influence tablet dissolution. All the batches complied with the Ph. Int specification since all six tablets used for each batch had a release content of more than 80% label claim within 30 minutes (Table 3).

Assay and Identification: The identification test is key in confirming the nature of the API in pharmaceutical products. The retention times of the fumarate salt, emtricitabine, and tenofovir disoproxil in the sample and standards used were concordant at 2.3, 3.1, and 11.8 minutes, respectively, as

shown in Table 4. All the batches, therefore, complied with the identification test and thus indicated the presence of the correct APIs in the dosage units.

For the assay, the sampled batches had emtricitabine content ranging from 96.68% to 100.85% while tenofovir disoproxil fumarate content ranged from 96.41% to 99.48% of the label claim. All the tablets therefore complied with the Ph. Int specifications of content between 90% and 110% of the label claim for both APIs.

Table 1. Macroscopic properties and packaging of emtricitabine/tenofovir disoproxil fumarate 200/300mg fixed-dose combination tablets.

Batch code	Manufacturer	Batch Number	Expiry Date	Shape	Colour	Tablet Imprint	Scorelines	Tablets per pack	Packaging	Physical defects
IB	Gilead Sciences, Germany	B425670 1	Jan 2025	Caplet	Light Blue	GILEAD	Absent	30	high-density polyethene (HDPE) bottle	No defect observed
C001	Mylan Laboratories Limited, India	3164230	Sep 2025	Caplet	Blue	M117	Absent	30	high-density polyethene (HDPE) bottle	No defect observed
C002	Mylan Laboratories Limited, India	3166410	Sep 2025	Caplet	Blue	M117	Absent	30	high-density polyethene (HDPE) bottle	No defect observed
C003	Mylan Laboratories Limited, India	3165072	Oct 2025	Caplet	Blue	M117	Absent	30	high-density polyethene (HDPE) bottle	No defect observed
C004	Mylan Laboratories Limited, India	3164076	Oct 2025	Caplet	Blue	M117	Absent	30	high-density polyethene (HDPE) bottle	No defect observed
C005	Mylan Laboratories Limited, India	3205697	Jan 2026	Caplet	Blue	M117	Absent	30	high-density polyethene (HDPE) bottle	No defect observed

IB – Innovator brand; C001-C005 – Generic brand batches

Table 2. Uniformity of weight, dimensions, hardness, and disintegration time of emtricitabine/tenofovir disoproxil fumarate 200/300mg fixed-dose combination tablets.

Batch Code	Average Retention Time (minutes) (n=6)			Average concentration (mg) per tablet (n . 6)		% Label Claim per tablet (n . 6)	
	Fumarate	Emtricitabine	Tenofovir Disoproxil	Emtricitabine	Tenofovir Disoproxil	Emtricitabine	Tenofovir Disoproxil
STD	2.301	3.158	11.815	-	-	-	-
IB	2.301	3.159	11.848	193.37 ±1.23	236.19 ±2.30	96.68 ±0.62	96.41 ±0.53
C001	2.301	3.159	11.858	201.69 ± 1.91	243.33 ±3.59	100.85 ± 0.95	99.32 ±1.47
C002	2.300	3.159	11.877	198.74 ±1.13	241.39 ±2.37	99.37 ±0.57	98.53 ± 0.97
C003	2.302	3.160	11.861	198.54 ±0.92	240.84 ± 0.75	99.27 ± 0.46	98.3 ±0.28
C004	2.302	3.159	11.846	201.56 ±2.30	243.73 ±3.46	100.78 ± 1.15	99.48 ± 1.41
C005	2.300	3.158	11.833	196.54 ±6.65	239.69 ±7.93	98.85 ±3.23b	97.83 ± 3.25

IB – Innovator brand; C001-C005 – Generic brand batches

Table 3. Dissolution of emtricitabine/tenofovir disoproxil fumarate 200/300mg fixed-dose combination tablets after 30 minutes.

Batch Code	% Dissolution at 30 minutes (n . 6)		Average concentration (mg) per tablet (n . 6)	
	Emtricitabine	Tenofovir Disoproxil	Emtricitabine	Tenofovir Disoproxil
IB	91.63 ±0.82	92.03 ±0.16	183.26 ±1.81	225.33 ±0.30
C001	93.48 ±1.91	92.16 ±0.08	186.96 ±3.82	225.46 ± 0.28
C002	89.67 ±0.80	92.67 ± 1.04	179.34 ± 2.52	227.05 ± 2.55
C003	91.25 ±0.94	90.66 ±0.06	182.50 ± 1.26	222.13 ± 0.16
C004	95.51 ±0.77	94.03 ± 2.23	191.02 ± 1.86	230.37 ± 5.46
C005	91.03 ± 1.21	91.37 ± 2.62	182.05 ± 3.24	223.70 ± 6.48

*Each tablet contains 300mg Tenofovir disoproxil fumarate equivalent to 245mg Tenofovir disoproxil

IB – Innovator brand; C001-C005 – Generic brand batches

Table 4. Retention times and assay of emtricitabine/tenofovir disoproxil fumarate 200/300mg fixed-dose combination tablets.

Batch Code	Average tablet weight (mg)	% Deviation from mean weight (n= 20)	Average tablet length (mm) (n=10)	Average tablet width (mm) (n=10)	Average tablet thickness (mm) (n=10)	Average tablet hardness (N) (n=10)	Disintegration time (minutes)
IB	1042.83	-1.02 - +1.88	19.23 ±0.15	8.76 ±0.08	7.12 ±0.03	265 ±14.05	03:24
C001	1044.29	-1.59 - +2.41	19.43 ±0.07	9.68 ±0.11	7.20 ±0.05	202 ±15.71	01:06
C002	1044.22	-1.54 - +1.87	19.45 ±0.12	9.72 ±0.08	7.21 ±0.06	192 ±23.17	02:37
C003	1037.42	-2.46 - +2.40	19.42 ±0.13	9.72 ±0.12	7.06 ±0.09	197 ±16.50	02:02
C004	1029.05	-1.55 - +2.33	19.44 ±0.08	9.66 ±0.10	7.16 ±0.07	182 ±21.31	02:11
C005	1037.81	-3.27 - +1.57	19.39 ±0.06	9.73 ±0.11	7.14 ±0.06	206 ±14.81	02:34

*Each tablet contains 300mg Tenofovir disoproxil fumarate equivalent to 245mg Tenofovir disoproxil

IB- Innovator brand; C001-C005 – Generic brand batches

Discussion

Both the innovator and generic emtricitabine/tenofovir disoproxil fumarate 200/300mg fixed-dose combination tablet batches sampled in the study complied with pharmacopeial specifications. Notably, the innovator and generic brands demonstrated pharmaceutical equivalence. Furthermore, all five batches of the generic brand complied with specifications, demonstrating intra-batch consistency. This observation reflects reliable manufacturing and quality control processes. These findings are contrary to a study done in Japan by Takizawa et al., (11) indicating generic and innovator brands of emtricitabine/tenofovir disoproxil fumarate 200/300mg fixed-dose combination tablets displayed differences in both the dissolution behaviors and in vitro membrane permeability tests.

Limitations

The study sample size of one batch of the innovator brand and five generic brand batches limits its statistical power. The small sample size was occasioned by time and resource constraints. Further, the single-time-point dissolution testing at 30 minutes limits the full characterization of dissolution profiles. Single-time point tests, though preferred as a routine quality control test, do not allow for comparison of product sameness.

Conclusions

The study aimed to evaluate and compare the quality of the innovator brand and batches of generic brand of emtricitabine/tenofovir disoproxil fumarate 200/300mg fixed-dose combination tablets used in Kenya. From the physicochemical analysis, all the sampled tablet brands/batches complied with the pharmacopeial specifications for uniformity of weight, hardness, disintegration,

identification, assay, and dissolution, and therefore can be considered to be of satisfactory quality.

Recommendations

Regular post-marketing surveillance of antiretrovirals and other medicines in Kenya will bolster market security and prevent proliferation by substandard and falsified medicines. Future studies employing larger sample sizes, dissolution profiling assessing multiple time points, as well as bioavailability and bioequivalence studies, will provide assurance of interchangeability of innovator and generic brands.

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The roadmap to enhanced availability of oral morphine solution in Kenya

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Background

Access to palliative care and pain relief is a health, equity, and human rights imperative that must be incorporated into the goal of achieving Universal Health Coverage (UHC). The Lancet Commission on Palliative Care and Pain Relief [1] recommends that countries' Essential Packages must ensure that both oral and injectable morphine preparations are available for any patient with moderate or severe pain or terminal dyspnea that cannot be adequately relieved by alternative means. The World Health Organization lists oral morphine solution (OMS) as an essential medicine. In Kenya, OMS is stocked in referral hospitals, primary care hospitals, as well as basic health centres in order to improve patient access [2].

Availability of oral morphine solution (prior to 2016)

A 2007 study on hospice and palliative care development in Africa [3] revealed major gaps in opioid availability and critical workforce development. Kenya was categorized as one of four African countries approaching integration of palliative services with the mainstream health system. However, despite the need for oral morphine solution by critically ill patients, there was no pharmaceutical product commercially available locally. This was against the backdrop of end-stage HIV disease, as well as a rising cancer burden, which further exaggerated the need for morphine. In Kenya, few health facilities would procure morphine powder and work with their pharmacy departments or local industries to formulate OMS. However, the OMS produced elicited queries on its quality, presence of sediments, shelf life, type of preservative used, as well as treatment outcomes for patients, hence the need to have a centralized national production unit.

Kenya Hospices and Palliative Care Association (KEHPCA) began advocacy in 2008/2009 to sensitize the healthcare system players on the need for centralized production of oral morphine, ensuring availability for patients, as well as address various myths around morphine use, e.g., its association with impending death, addiction fears, among others. The Ministry of Health (MOH), Kenya, appreciated the dire need for a consistent supply of oral morphine solution to patients across the country. The first step in ensuring morphine access was addressing policy issues that would inadvertently be encountered. Secondly, morphine is a controlled drug that would require legal aspects and restricted access protocols to be laid out in partnership with the regulatory authorities. Thus, MOH - Kenya carried out health care worker, patient, and community-level advocacy to enhance morphine acceptability. This advocacy aimed to address barriers to morphine use, such as lack of knowledge and fear of prescribing at the health care worker level, as well as concerns about side effects at the patient and community level.

By this time, Uganda already had an ongoing production of oral morphine solution at Hospice Africa Uganda, headquartered in Kampala. In 2013, a team from Kenyatta National Hospital (KNH) and MOH- Kenya conducted a site visit to Uganda to benchmark with the Uganda manufacturing facility with support from the Treat the Pain (TTP) program - A program of the American Cancer Society and KEHPCA. Thereafter, MOH- Kenya gave the go-ahead for the project.

Pilot production of oral morphine solution at KNH pharmaceutical manufacturing unit (2016)

The KNH manufacturing unit, then defunct, was selected as the production site for oral morphine solution after its renovation. A team from Hospice Africa Uganda visited the proposed manufacturing unit and participated in a trial run of the manufacturing process using the non-automated equipment at hand. This trial run, without active ingredient/ excipients, enabled identification of potential gaps and informed mitigation measures. Thereafter, the School of Pharmacy - University of Nairobi (SoP–UoN) provided technical assistance to the project, owing to the staff's expertise in pharmaceutical product development. Two departments at SoP-UoN, namely 'Pharmaceutics and Pharmacy Practice' and 'Pharmaceutical Chemistry' were co-opted into the project. The 'Pharmaceutics and Pharmacy Practice' department provided guidance with regard to preformulation, formulation development, drafted requisite production documents (master formula; batch manufacturing record templates, batch packaging record templates, standard operating procedures), visited the manufacturing unit to advise on its suitability, compliance with Good Manufacturing Practices, and overall quality assurance. The 'Pharmaceutical Chemistry' department provided expertise on quality evaluation protocols that would be instituted. The quality analysis of the raw materials, water, and finished products was performed at the Drug Analysis and Research Unit (DARU), an analytical lab at SoP-UoN affiliated to the 'Pharmaceutical Chemistry' department. KEHPCA, through a grant from the American Cancer Society, provided a reverse osmosis water purification system and procured required excipients. Danish International Development Agency (DANIDA) through a grant to Kenya Medical Supplies Agency (KEMSA), provided funding for the purchase of the first batch of morphine powder for production (47 kilograms).

The collaborative multi-sectoral team consisting of MOH, KNH, SoP-UoN, and KEHPCA held several consultative meetings to plan the project inception. The team selected two strengths of oral morphine solution for production: an adult strength of 10mg/mL and a paediatric strength of 1mg/mL. The products were to be packaged in 100 mL coloured plastic bottles and distinctly labelled with different features to avoid mix-ups of the two dosage strengths. Furthermore, production of the two strengths was to be performed on different shifts/days, and the respective documentation and packaging materials were segregated.

Due to the controlled nature of morphine, pre-formulation and formulation development were guided via computational design of experiments and extensive literature review. The pilot production comprising a batch size of 50L of adult strength morphine (10mg/mL), which was packaged into 100mL bottles, was carried out in September 2016. The production yield was 98.8%. Major challenges encountered were the time and labour-intensive nature of the production process due to the lack of automation of the bottle filling/packaging process. Quality evaluation tests on the resultant morphine solution, including physical appearance (clear, colourless solution), pH (4.7), volume (100mL), chemical assay (100.1%), and microbial load (aerobic count <1000 cfu/mL; yeast and moulds <100 cfu/mL), performed at DARU, SoP-UoN, met the requisite in-house specifications. Stability studies indicated that the morphine solution was stable for four weeks at room temperature.

This successful pilot production heralded a milestone opportunity with the prospect of scale-up of production to meet the national demand whilst ensuring standardization of the quality of OMS utilized locally. The KNH pharmaceutical manufacturing unit (KMPU) housed within the Pharmacy Department provided this opportunity.

Large scale production of oral morphine solution at KNH pharmaceutical manufacturing unit (2016-2024)

Following the success of the pilot scale OMS production and introduction of a semi-automated bottle-filling and capping machine, to further optimize the process, large-scale OMS production at KMPU commenced in late 2016. Large-scale production of morphine solution comprised batch sizes of 1500L for the adult strength (10mg/mL) and 500L for the paediatric strength (1mg/mL) formulations. These production cycles were scheduled as guided by county demand, with production occurring as frequently as bimonthly.

MOH, KEHPCA were involved in policy, planning, and resource mobilization, while KEMSA procured and facilitated the delivery of morphine powder to KMPU. The production process at KMPU would involve staff from both KNH and SoP-UoN, with the latter providing Quality assurance and Quality control functions. After production of the morphine solution at KMPU, KEMSA would collect the finished pharmaceutical product (OMS) for delivery to their central store and thereafter distribution to health care facilities nationwide. The KEMSA logistics and management information system (LMIS) facilitated supply chain operations and controlled the flow of both morphine powder and oral morphine solution.

The MOH-Kenya, through the National Cancer Control Program, installed a larger capacity reverse osmosis water purifier in June 2022 to improve production turn-around time. The program also set up the National Oncology Dashboard, where facilities would place their orders for oral morphine solution. The successful production of morphine solution for nationwide use has been ongoing since 2016, ensuring a reliable supply of the finished product to patients throughout the country. The KEHPCA annual reports [4]

indicate that OMS production has been increasing annually, with 27,000 (24,000 – adult strength; 3,000 – paediatric strength) bottles of OMS produced in 2023.

Challenges encountered and way forward

The outstanding success of the project has ensured access to quality oral morphine solution by patients nationally. Routine challenges faced included the worldwide shortage of morphine powder, with national stockouts being reported in 2019-2020 [5]. The exorbitant cost of morphine powder also directly impacts the production schedule. The possibility of out-of-specification results is a ubiquitous challenge within the industry life cycle of all pharmaceutical products.

Each of these challenges requires a unique approach to solve. To address the periodic shortage/stockouts of OMS, strengthening of the LMIS system, reliable and sustainable supply of morphine powder and excipients based on annual forecasts, timely reporting by health facilities, as well as ensuring a buffer stock of morphine powder at the national level, is recommended. To mitigate the expense at the patient level, the cost of OMS can be subsidized, particularly for patients with chronic/terminal conditions. Prevention of out-of-specification results can be ensured by strengthening technical expertise in industrial pharmacy, emphasizing Good Manufacturing Practices, designation of prequalified, dedicated production units, and regular personnel training. Critically, ad-hoc production of OMS by independent facilities without quality assurance procedures or stability data should be highly discouraged.

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