GOLD STANDARD MEDICINES FOR AI-DRIVEN DRUG REGULATION IN AFRICA: A RAPID DATA LANDSCAPE REVIEW

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REPORT TO THE GATES FOUNDATION

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FEBRUARY 2025

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INTRODUCTION

The ability of African National Regulatory Agencies (NRAs) to efficiently review and approve drug dossiers is critical to ensuring timely access to essential medicines across the continent.[1,2] To streamline these processes, there is increasing interest among African NRAs and external stakeholders in leveraging artificial intelligence (AI) to optimize regulatory processes.[3] In order to progress toward the use of AI for drug regulation across Africa, an understanding of the availability and quality of data for widely used and essential drugs across the continent is needed.

The Gates Foundation engaged the START team to inform future AI applications in African NRAs through the identification of "gold standard" drugs in four identified therapeutic areas: **malaria**, **tuberculosis (TB)**, **human immunodeficiency virus (HIV)**, and **women's health**. For each gold standard drug selected, the availability of structured, high-quality data that could be used to support AI-driven regulatory review was assessed. In addition to selecting a primary gold standard drug for each therapeutic area, backup compounds were also identified to ensure flexibility in regulatory applications.

This report outlines the selection and justification of gold standard drugs and backup compounds, quantification of data availability, and identification of high-quality sources to support AI-based dossier review. The team conducted a rapid review of clinical trials, pharmacokinetic and pharmacodynamic (PK/PD) data, post-market safety reports, and regulatory approvals to assess the accessibility and availability of structured datasets for future AI applications. Through mapping existing data availability and identifying key gaps, the findings of this report highlight opportunities to strengthen AI-readiness in drug regulation, particularly for widely used essential medicines across Africa.

METHODS

Selection of Therapeutic Areas

The therapeutic areas of malaria, TB, HIV, and women's health were selected based on the client's priorities. A gold standard drug and backup compound were identified for each area in alignment with the client's focus and to ensure flexibility in regulatory applications.

Selection of Gold Standard and Backup Drugs

A preliminary search of drug-related metrics was performed to inform development of standardized criteria for gold standard and backup compound selection. Data related to pharmacokinetic and pharmacodynamic (PK/PD) properties, clinical efficacy and endpoints, drug safety, real-world effectiveness, and drug accessibility were reviewed with consideration for the African context and evaluated as metrics for data quality and availability. Due to variability between the four therapeutic areas, no strict quantitative cutoffs were set for any metrics to allow for flexibility and nuance in compound selection. These metrics were also used for later evaluation of high-quality sources.

Based on this initial review, World Health Organization (WHO)-recommended medicines and first-line treatments were prioritized for gold standard and backup compound selection.[4] Combination therapies were assessed as a single unit when possible, and the backbone of the combined treatment was assessed otherwise. Aside from these considerations, selection of gold standard and backup compounds was performed independently for each therapeutic area due to differences in treatment modalities or other contexts.

Additional selection criteria were identified for individual therapeutic areas. Contraceptives were prioritized for women's health due to their relevance to the Foundation's work and their widespread implementation. Treatments for active TB were prioritized over those for latent TB. Pre-exposure prophylaxis (PrEP) treatments and newer therapies expected to outperform and replace existing options, including new long-acting injectables, were included in consideration for the HIV gold standard.

METHODS (CONT.)

Quantification of Data Availability

Once compounds were selected for each therapeutic area, the following data availability metrics were quantified for each gold standard drug and extracted into an Excel spreadsheet:

- ✓ Total number of randomized clinical trials, number of randomized clinical trials conducted in Africa, and a list of African countries in which those trials were performed according to ClinicalTrials.gov
- ✓ Number of randomized clinical trial and systematic review publications in the PubMed database
- ✓ Number of health or regulatory guidelines available, as identified through the WHO Guidelines Repository.
- ✓ Number of post-market safety reports in the WHO VigiAccess, U.S. Food and Drug Administration (FDA) Adverse Reporting System, and European Medicines Association (EMA) EudraVigilence databases
- ✓ Number and list of African country approvals*
- ✓ Number, list, and years of approvals in authoritative global regulatory agencies, such as the WHO, FDA, and EMA

Based on these quantitative metrics, each drug was assigned a data availability score of high, medium, or low based on the following criteria:

Data Availability Score Criteria

	Randomized Clinical Trials	Publications	Global Guidelines
High	>60	≥ 150	>80
Medium	30-60	50-150	40-80
Low	<30	<50	<40

**Quantification of African country approvals was limited by lack of publicly-available online information for many African NRAs. In the absence of information from NRA websites, other sources, including country-specific guidelines, policies, and publications, were used to confirm in-country use and subsequently infer approval. Not all additional sources were thoroughly verified due to time constraints.*

Identification of High Quality Sources

In addition to quantification and evaluation of data availability, 2-4 high-quality sources were identified for each gold standard compound. Clinical trials, guidelines, systematic reviews, meta-analyses, regulatory or pharmacovigilance reports, publications, and databases were considered. Sources were deemed high-quality based on their inclusion of the relevant drug metrics identified in our initial metrics review. These include:

- ✓ General drug information, such as administration route and clinical trial completion
- ✓ Efficacy data, such as efficacy rate and duration of effect
- ✓ PK/PD data, such as half-life, bioavailability, and dosing frequency
- ✓ Safety data, such as adverse event rates and availability of post-market safety data

Source metadata, which metrics it includes, and detailed notes on its data availability and AI-readiness were extracted into an Excel spreadsheet. AI-readiness was assessed based on formatting and presentation of relevant data. Clear tables with easily-extractable information were considered more AI-ready than data weaved into text or more complex figures.

JUSTIFICATION FOR GOLD STANDARD AND BACKUP DRUGS

MALARIA

According to the WHO, artemisinin-based combination therapy (ACT) is the gold standard for malaria treatment, offering the most effective response to P. falciparum, the deadliest form of the disease.[5] Used for over 20 years and widely adopted across Africa, ACTs help prevent drug resistance, which has rendered many past treatments ineffective.[6] Their proven efficacy and broad use made them the clear starting point for selecting gold standard and backup malaria therapies.

Gold Standard: Artemether- lumefantrine (AL)

Artemether-lumefantrine (AL, brand name Coartem) is a widely used ACT recommended by the latest WHO Guidelines for uncomplicated malaria.[7] Added to the WHO Essential Medicines List in 2002 and pre-qualified in 2004, it has been used globally for over two decades.[8] AL has key advantages over other ACTs: lumefantrine has never been available as monotherapy, reducing resistance risk, and it demonstrates increased drug exposure when co-administered with lopinavir-based antiretroviral therapies (ARTs) without added toxicity, ensuring its safety for HIV co-infected patients.[7] It is also now recommended for all uncomplicated malaria in the United States, including during pregnancy.[9] Its long-standing efficacy and extensive data availability make it an ideal malaria gold standard for AI model development.[10,11]

Backup: Artesunate- pyronaridine

Artesunate-pyronaridine (ASPY, brand name Pyramax) is a novel ACT performing as well or better than AL in efficacy and safety.[12] Included in WHO guidelines as a first-line ACT for uncomplicated malaria[7], ASPY has less data due to its recency but holds promise for AI integration in drug regulation. However, its altered pharmacokinetics in certain groups (e.g., pregnant women, young children, HIV co-infected patients) make AL the preferred gold standard, positioning ASPY as a strong backup option.[7]

TUBERCULOSIS (TB)

The WHO-recommended first-line TB regimen combines multiple drugs to prevent resistance and ensure efficacy.[7] Isoniazid and rifampicin are key medications, widely used together across Africa.[13] Despite the prevalence of combination therapy, isoniazid was designated the gold standard due to its central role, broad availability, and use as a standalone treatment for latent TB.

Gold Standard: Isoniazid

Isoniazid, a bactericidal agent that inhibits mycolic acid synthesis, is highly effective against *Mycobacterium tuberculosis* and plays a key role in TB treatment.[14,15] It is a core component of first-line TB regimens and is also used alone for latent TB prevention, particularly in high-risk groups like people living with HIV.[14,16,17] Listed on the WHO Essential Medicines List, isoniazid is widely available across Africa, demonstrating its importance in TB control efforts.[7] Its well-documented safety profile, extensive clinical trial data, and strong regulatory history make it a reliable and well-established treatment.[14,17,18] While rifampicin is equally essential, isoniazid's dual role in active and preventive therapy, broad availability, and long-standing efficacy made it the preferred gold standard for this review.

Backup: Rifampicin

Rifampicin, a bactericidal antibiotic, is essential in first-line TB regimens, shortening treatment duration, improving adherence, and reducing relapse risk.[13,19,20] Included in the WHO Essential Medicines List, it is widely available across Africa but requires combination therapy to prevent resistance and interacts with HIV antiretrovirals (ARVs).[7,13,21] While both drugs are crucial, isoniazid's role in both active and preventive TB therapy, long-term safety, and standalone use made it the preferred gold standard, with rifampicin as a strong backup.

JUSTIFICATION FOR GOLD STANDARD AND BACKUP DRUGS (CONT.)

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

HIV treatment and prevention require distinct approaches, with ART for those living with HIV and PrEP for prevention.[22] Dolutegravir-Lamivudine-Tenofovir (TLD) was selected as the gold standard for treatment due to its widespread adoption, strong safety profile, and high barrier to resistance. Lenacapavir, a promising long-acting injectable for PrEP, was chosen as the backup for its potential to improve adherence, though it is not yet widely adopted.

Gold Standard: Dolutegravir-Lamivudine-Tenofovir

TLD is the WHO-recommended first-line treatment for HIV in LMICs, where the disease burden is highest.[23,24] Included on the WHO Essential Medicines List, it is preferred for its affordability, once-daily dosing, and single-pill formulation, which enhance cost-effectiveness and adherence.[7,25] Safe for pregnant women and children, it is well-suited for resource-limited settings.[26,27,28] Following WHO endorsement, PEPFAR and national regulators approved its use and listed it as an essential medicine.[29] TLD was selected as the HIV gold standard due to its widespread adoption, strong safety profile, and high barrier to resistance, making it the most widely used ARVs globally and a reliable option for large-scale HIV programs.[30,31]

Backup: Lenacapavir

Lenacapavir is a twice-yearly injectable HIV-1 capsid inhibitor with 100% efficacy in trials and is under evaluation for use as PrEP.[32] Its long-acting formulation addresses adherence challenges associated with daily oral PrEP, including stigma, pill fatigue, and inconsistent access.[33] While not yet WHO-approved, pending the PURPOSE 2 trial, it is undergoing assessment for efficacy, safety, cost-effectiveness, and scalability.[34,35,36] It was selected as a backup due to its strong potential but limited current adoption.

WOMEN'S HEALTH

The Levonorgestrel IUD, Etonogestrel implant, and DMPA-SC are all highly effective contraceptive methods that have been widely used for decades. These options were selected for their proven efficacy, safety, and widespread use in global women's health programs. Their classification as gold standard and backup therapies is based on their reliability, data availability, and long-term effectiveness.

Gold Standard: Levonorgestrel IUD

The Levonorgestrel-Releasing IUD (LNG-IUD) is considered the gold standard in intrauterine contraception due to its high efficacy, lasting up to 5 years, and low risk of side effects.[37] It is a preferred method worldwide, especially in countries with limited access to other forms of contraception.[38] The LNG-IUD is highly effective, with a failure rate of less than 1%, and its hormone release can help with heavy menstrual bleeding, making it a very common choice for contraception.[39]

Backup: Etonogestrel Implant

The Etonogestrel implant (brand name Nexplanon) is a highly effective, long-acting reversible contraceptive (LARC) that provides up to three years of pregnancy prevention.[7] As a progestin-only method, it is a suitable option for individuals who cannot use estrogen-based contraception. With a failure rate of less than 1%, it offers strong protection, though it is often considered a backup to the levonorgestrel-releasing IUD due to slightly higher complication rates, such as irregular bleeding and unpredictable menstrual changes.[38] Despite these factors, its ease of use, reliability, and ability to provide long-term contraception with minimal user intervention make it an important backup option.

Backup: DMPA-SC (Sayana Press)

DMPA-SC (Sayana Press) is a subcutaneous injection of depot medroxyprogesterone acetate, offering effective contraception for up to 3 months.[40] It is a reliable backup option due to its low failure rate (less than 1%) and ability to be self-administered, making it especially valuable in resource-poor settings.[41] However, it may cause side effects like weight gain and menstrual changes, which can make it less preferable compared to the LNG-IUD or implant.[42]

Artemether- lumefantrine (AL)
AL was found to have a high level of data availability, with 131 clinical trials conducted globally, including 104 trials in Africa.[43] The drug has been pre-qualified by the WHO since 2004 and is a mainstay in malaria treatment, underscoring its proven efficacy and the volume of supporting data from multiple African nations.[7] Safety and adverse event data reports include over 2,164 reports from the WHO VigiAccess database, 364 cases from the FDA Adverse Event Reporting System (FAERS), and 520 reports from the EMA.[44,45,46]

Isoniazid
Isoniazid was found to have extensive data availability, with 117 clinical trials conducted globally, including 68 trials in African countries such as Kenya, South Africa, and Botswana.[43] The drug has been a core component of first-line TB treatment for decades and has been included on the WHO Essential Medicines List since 1977.[7] Its safety and efficacy are supported by 83,935 adverse event reports from major pharmacovigilance databases, including the WHO VigiAccess system, the FDA, and the EMA.[44,45,46] Isoniazid's strong regulatory history and widespread use highlight its long-standing importance in TB treatment programs across Africa.

Dolutegravir-Lamivudine-Tenofovir (TLD)
TLD was found to have a substantial level of data availability, with 60 clinical trials conducted globally, including 21 trials in African countries such as Kenya, South Africa, Uganda, and Nigeria.[43] The drug is included in the WHO Essential Medicines List and has been approved as the first-line antiretroviral therapy in many LMICs.[7] Its safety profile is well-documented, with 13,382 adverse event reports recorded in the WHO VigiAccess database.[44] While widely used in Africa, the fixed-dose combination of TLD remains pending approval in higher-income countries.[47]

Levonorgestrel- Releasing Intrauterine Device (IUD)
The LNG- IUD was found to have a moderate level of data availability, with 46 clinical trials registered globally, including seven trials conducted in African countries such as South Africa, Kenya, Egypt, Swaziland, and Zambia.[43] The LNG-IUD has been included on the WHO Essential Medicines List since 2007 and has regulatory approval from 16 different African NRAs.[7] Safety and adverse event data are substantial, with over 287,000 reports from the WHO VigiAccess database, 221,797 cases from FAERS, and 108,308 reports from the EMA.[44,45,46] This dataset highlights the extensive safety monitoring of the LNG-IUD globally, though its usage across Africa remains relatively low.

Gold Standard Drug Availability Scores

	Randomized Clinical Trials	Publications	Global Guidelines	Data Availability Score
Artemether- lumefantrine (AL)	131	375	80	High
Isoniazid	117	676	290	High
Dolutegravir-Lamivudine-Tenofovir (TLD)	60	*N/A	121	High
Levonorgestrel- Releasing Intrauterine Device (IUD)	46	156	46	Medium

**The estimated count of TLD publications is high, but many studies analyze only two of the three drugs in combination, making it difficult to isolate those specifically on TLD. Due to time constraints, the team could not manually verify each publication for accuracy.*

IDENTIFICATION OF HIGH- QUALITY SOURCES

The START team identified high-quality sources for each gold standard drug individually, ensuring that each selected drug had multiple sources of structured data. For example, FDA reports for three different drugs were each counted as separate sources, as they are published on separate pages and provide distinct regulatory and safety data for each gold standard drug. Across all therapeutic areas, the team identified 2–4 high-quality sources per drug, covering key metrics encompassing PK/PD, efficacy, and post-market safety data. The high-quality sources, further documented in the project spreadsheet, offer a strong foundation for AI-driven regulatory workflows for the identified gold standard drugs; however, the gaps in structured datasets remain a barrier to the automation of dossier review for widely used drugs in Africa. Full citations for all high-quality sources identified in this review are provided in the appendix.

The FDA was identified as the strongest source of structured regulatory data; however, its applicability is limited for drugs only approved and utilized in Africa. For example, TLD, despite its widespread usage across Africa, is not FDA-approved as an HIV treatment in the United States, limiting the ability to extract regulatory and post-market safety data on TLD from this source.[47] In contrast, artemether-lumefantrine and the LNG- IUD are recent and FDA-approved, allowing for strong, structured datasets from the FDA's publications, despite being a U.S. -based source. However, detailed approval summaries are not available for many older drugs, including isoniazid, which was approved in 1953.[48] The FDA does provide labeling information for isoniazid, outlining its indications, dosage, and safety, although not in structured format.

Across all identified high-quality sources, systematic reviews and meta-analyses provided the most structured, AI-suitable data. The rapid review identified 2 clinical trials, 2 regulatory reports, 3 systematic reviews, and 4 meta-analyses containing relevant and AI-suitable data. These sources frequently present key metrics in table format, making them easier to extract and standardize for AI applications. However, there remains a significant gap in publicly available, structured datasets on PK/PD, efficacy, and post-market safety for essential medicines in Africa. This lack of AI-ready datasets presents a challenge for automating regulatory review but might serve as an opportunity for investment. A structured data initiative could bridge this gap by developing a centralized, AI-compatible database for essential medicines in Africa.

GAPS AND LIMITATIONS

Despite extensive efforts to quantify data availability and identify high-quality sources, several challenges limited the ability to review AI-readiness across all selected drugs. Key barriers included gaps in publicly available structured datasets, lack of transparency in African NRA approvals, and inconsistencies in regulatory documentation for commonly used medicines. The following limitations outline constraints encountered during the data collection process, as well as challenges in integrating AI into drug regulatory workflows.

- **Challenges in Identifying AI-Ready Datasets:** There is no single publicly- available consolidated source that compiles structured data on these drugs widely that are in Africa used, making it difficult to extract standardized information across key metrics, such as PK/PD, efficacy, and post-market safety.
- **Limited Transparency in African NRA Approvals:** Many African NRA websites lack publicly available information on which drugs are officially approved, making it challenging to verify regulatory status.
- **Unclear Approval Processes for Commonly Used Drugs:** Some drugs are widely used across multiple countries despite no explicit record of approval, raising questions about their individual regulatory pathways and what data were used to justify their implementation.
- **Formulation Changes Limits Data Availability:** Some essential medicines in Africa, such as TLD, have undergone formulation changes over time, making it difficult to distinguish past regulatory submissions from newer versions.

FINAL RECOMMENDATIONS

1. Create structured, AI-suitable datasets of essential medicines in Africa to improve regulatory efficiency across the continent. Despite the widespread use of the identified gold standard drugs, publicly available structured data remains a major gap.
2. Improve access to proprietary datasets from pharmaceutical companies and global regulatory agencies. Establishing partnerships or data-sharing agreements could enhance AI applications by incorporating richer clinical and safety data not currently available to the public.
3. Expand the availability of regional regulatory data by encouraging NRAs to publish structured approval and pharmacovigilance data. A centralized dashboard could streamline data access across multiple African regulatory agencies.
4. Develop a standardized reporting framework for NRAs to systematically document drug approvals, clinical trial data, and post-market safety reports, ensuring consistency and future AI-readiness.
5. Support African NRAs in integrating AI into regulatory processes by leveraging regional regulatory bodies rather than working with individual NRAs. This could improve harmonization across multiple countries.

CONCLUSION

The findings of this report demonstrate both the strengths and limitations of existing data for essential medicines in Africa, providing insights into the feasibility of AI-driven regulatory processes. While the selected gold standard drugs for malaria, tuberculosis, HIV, and women's health have been extensively studied, the availability of structured, AI-ready datasets remains inconsistent across key metrics such as pharmacokinetics, efficacy, and post-market safety. In particular, limited transparency from African NRAs and the absence of centralized regulatory data pose challenges. Addressing these gaps will require greater investment in structured data initiatives, improved reporting standards among regulatory agencies, and expanded collaboration with proprietary data sources, including pharmaceutical companies and global regulatory bodies. Strengthening data standardization and accessibility will be essential to using AI for regulatory decision-making and ensuring timely access to essential medicines across Africa.

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