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Artificial intelligence in human immunodeficiency virus mutation prediction and drug design: Advancing personalized treatment and prevention

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ABSTRACT

Despite significant advancements in highly active antiretroviral therapy (HAART), Human Immunodeficiency Virus (HIV) remains a global health challenge due to its high mutation rate, drug resistance, and the complexity of treatment optimization. Artificial intelligence (AI) has emerged as a transformative tool in HIV research, offering innovative solutions for predicting viral mutations, optimizing drug discovery and formulation design. However, challenges such as limited access to diverse datasets, ethical concerns, and model interpretability hinder the full potential of AI in HIV research. This review highlights gaps in AI-driven HIV research and explores advancements to address these challenges. AI-driven platforms, such as DeepHIV and geno2pheno, have demonstrated success in forecasting resistance mutations and guiding therapeutic decisions. AI is also revolutionizing drug formulation development by enhancing solubility, bioavailability, and stability, while improving patient adherence through advanced delivery systems. Current applications of AI in HIV mutation prediction, drug discovery, and formulation optimization have highlighted the potential of AI towards HIV management and eradication while addressing gaps in data availability and model transparency. By integrating structural, pharmacological, and clinical data, AI provides a comprehensive framework for rational drug design and personalized treatment strategies. By leveraging AI-driven insights, HIV treatment and prevention can become more personalized, efficient, and sustainable. Future research should focus on overcoming data limitations, enhancing model interpretability, and exploring innovative AI approaches to contribute to the global fight against the HIV epidemic.

1. Background

The Human Immunodeficiency Virus (HIV) remains one of the most significant public health challenges worldwide, affecting over 39.9 million people globally as of the end of 2023 with new infections account for about 1.3 million new infections in 2023 [1]. The virus has led to a devastating epidemic with profound health, social, and economic impacts, particularly in low- and middle-income countries where the burden of HIV/AIDS is disproportionately high [2]. About 630000 HIV-positive people lost their lives to HIV-related health problems [3]. Advancements in HIV prophylaxis and management have markedly improved prevention and treatment outcomes, contributing to a global decline in infection rates and HIV-related deaths [4–6]. Currently, about 86% of people know their HIV status and about 30.7 million people living with HIV (PLWHIV) are currently on antiretroviral medications globally [7]. In sub-Saharan Africa, the lifetime risk of HIV infection dropped by 60% from 1995 to 2021 [8]. However, challenges remain in regions like Central Europe, eastern Europe, and Central Asia, where infection rates have risen. Moreover, the achievement of the 95-95-95 goal by the end of 2025 as well as the World Health Organization (WHO), global fund and UNAIDS's sustainable development goal (SDG)

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Abbreviations

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
UNAIDS	Joint United Nations Programme on HIV/AIDS
AI	Artificial Intelligence
ML	Machine learning
DeepHIV	Deep Learning for HIV Drug Resistance Prediction
geno2pheno	Genotype to Phenotype Prediction Tool
AUC	Area Under the Curve
CNN	Convolutional Neural Network
ANN	Artificial neural network
MLP	Multilayer perceptron
BRNN	Bidirectional recurrent neural network
SVM	Support vector machines
GNN	Graph neural network
GAN	Graph Attention Network
HIV Env	HIV-1 envelope glycoprotein
HTS	High-throughput screening
NLP	Natural language processing
LMs	AI-powered language models
NLP	Natural language processing
QSAR	Quantitative Structure-Activity Relationship
GRNNs	Generalized regression neural networks
RT	Reverse transcriptase
GCN	Graph Convolution Network
MPNN	Message Passing Neural Network

of ending HIV epidermic by 2030 seems far-fetched [9]. Continued efforts in prevention, treatment accessibility, and testing are essential to meet global health targets [10,11].

HIV's dynamic nature presents unique challenges to its control and eventual eradication. The virus's high replication rate, combined with the error-prone activity of its reverse transcriptase enzyme, results in a rapid accumulation of genetic mutations. This genetic variability allows HIV to evade the host's immune system and develop resistance to antiretroviral drugs, necessitating constant adaptation of treatment strategies [12]. Also, HIV's ability to integrate into the host genome, create latent reservoirs that are impervious to current therapies, represents a major obstacle to achieving a cure [13,14].

Artificial intelligence (AI) has emerged as a promising tool, offering novel solutions to tackle the complex challenges associated with HIV at different stages (Fig. 1). From understanding the HIV viral mechanisms, to diagnosis, preventive strategies, predicting viral mutations, optimizing drug development, and enhancing personalized treatment regimen [15], AI is revolutionizing healthcare by offering advanced solutions to complex problems through methods like machine learning (ML), deep learning, and natural language processing. These technologies enable AI to recognize patterns, make predictions, and support data-driven decision-making, ultimately improving the accuracy and efficiency of healthcare interventions [16–18]. Despite the advancements recorded with AI predictive modelling, addressing its restrictive capability of artificial neural network in novel formulation prediction and optimization due to lack of robust datasets is crucial to ensure accuracy, interpretability and multidisciplinary use. Lack of quality diverse datasets capable for diverse training of algorithms involving multiple parameters often lead to suboptimal performance and limited applicability. Data augmentation by synthetic data generation, imputation and bias correction are essential for enhanced model robustness. Integrating multiple data representations and neural network architectures by collaboration between pharmaceutical companies, regulatory bodies and research institutes is also essential [19]. Challenges with difficulty in interpreting AI decision making process due to lack of transparency results in poor acceptance and adoption of AI predictive modelling in critical drug formulation development and acceptance of formulations for clinical use remains a challenge [20]. This review aims to bridge these gaps by providing a comprehensive analysis of recent advancements in AI applications for HIV research.

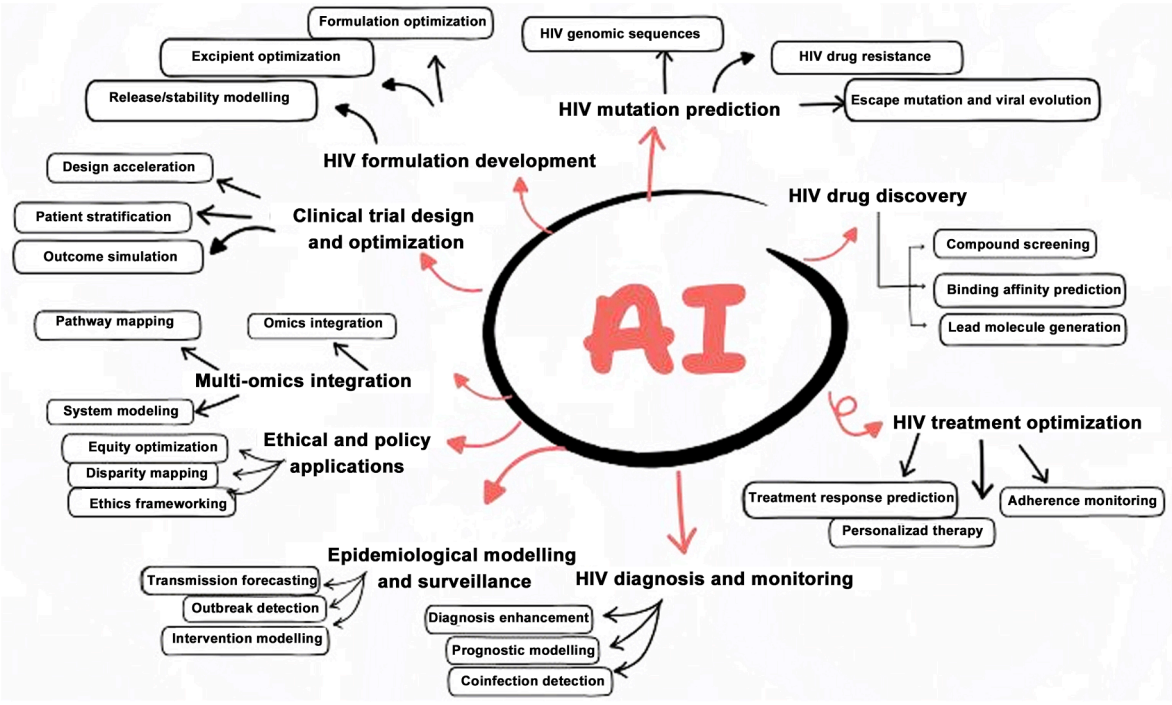

Fig. 1. The multifaceted roles of AI across key domains of HIV research and management.

Specifically, it focuses on examining how AI models have been utilized to analyze genetic data to forecast mutations associated with drug resistance, and AI's contributions to accelerating drug development, including virtual screening, design of novel therapeutics and optimization of drug dosage forms. By highlighting emerging trends and outlining a clear roadmap for the integration of AI in HIV research, this work seeks to contribute to the development of innovative and effective strategies that advance the global fight against HIV/AIDS.

2. HIV viral mutations and treatment resistance

HIV management is impacted by challenges such as the high mutation rate of the virus, leading to the emergence of drug-resistant strains, the complexity of tailoring treatment regimens to individual patients, and the need for continuous monitoring of treatment efficacy and adherence. These factors complicate ongoing efforts to effectively curb the scourge of this epidemic. AI offers a promising avenue to overcome many of these obstacles, including the prediction of viral mutations, the optimization of drug development, and the personalization of treatment regimens [21].

2.1. AI for prediction of HIV viral mutations

HIV's replication process is inherently error-prone due to the lack of proofreading activity in its reverse transcriptase enzyme [22,23]. This results in frequent genetic mutations during each replication cycle. These mutations contribute to the virus's extraordinary genetic diversity, allowing it to evade immune responses and adapt to antiretroviral therapy [12,21]. The development of drug resistance is a direct consequence of this rapid evolution, as selective pressure from therapy favors the survival of resistant strains [24,25]. While traditional bioinformatics relies on rule-based algorithms, AI offers dynamic and adaptive solutions. AI models improve prediction accuracy and scalability, addressing limitations of conventional methods [26,27].

By analyzing genomic data, AI can predict viral mutations and resistance, allowing for proactive adjustments in treatment. ML and neural networks, deep learning-based predictors analyze viral genetic sequences to identify patterns indicative of potential mutations [28]. These models learn from extensive datasets, including genetic, clinical, and structural datasets, enabling predictions with high accuracy. AI-driven platforms, such as DeepHIV and geno2pheno, have demonstrated success in predicting resistance mutations [29]. These systems provide insights that guide treatment decisions, enhancing patient care. Machine learning models have demonstrated a broad range of predictive performance in HIV drug resistance and mutation prediction tasks. Yilmaz et al. reported. model prediction accuracy of 0.774 and Area Under the Curve (AUC) of 0.859 [30]. Al-Amran et al. also reported model accuracy scores for mutation prediction of 0.850 by 2020 to 0.950 by 2023 [31]. Reported graph neural network model predication accuracy values reported by Di Teodoro span from 0.489 to 0.835 [32], while the model utilized in another study which compared models encompassing history (H) with one without (NH) highlighted that H-model exhibits better discriminative performance, achieving a higher ROC-AUC score of 76.34% compared to 74.98% observed for the NH-model [33]. Hie et al. reported discriminative accuracy, performance of the prediction model varies from very strong for Spike (0.85), to moderate for HIV Env BG505 (0.64), and weak for Spike RBD (0.57) [34]. Notably, models such as convolutional neural network (CNN) outperformed others, with accuracy ranging from 86.2% to 95.9%, while multilayer perceptron (MLP) and bidirectional recurrent neural network (BRNN) ranged from 65.9 to 94.6% and 72.9–94.6%, respectively, based on 5-fold cross-validation [35]. The regression-based artificial neural networks (ANNs) developed by Sheik Amamuddy et al. showed outstanding predictive accuracy for almost all antiretroviral drugs, with average R^2 values surpassing 0.95 and exhibiting low variability. This highlights their strong precision and dependable performance in modeling drug resistance profiles [36]. Heider et al. reported, AUC values ranging from 0.6819 to 0.9119 predictive performance of the model(s) across different datasets or drug resistance labels, reflecting moderate to excellent performance depending on the dataset or task [37]. Table 1 summarizes these studies that utilize AI driven approach for HIV mutation and resistance pattern prediction. A consistent trend across these studies is the wide adoption of machine learning models, particularly neural networks, support vector machines, and random forests for analysing viral genetic sequences. Additionally, the fusion of genomics with AI, as shown in multiple studies, underscores a shift towards precision public health where treatment and prevention strategies are increasingly informed by real-time data and predictive analytics [38–41].

3. AI-driven HIV drug discovery

Drug development has long been recognized as a multifaceted and lengthy process, involving extensive research, rigorous testing, and a substantial amount of trial-and-error experimentation. This traditional approach relies heavily on the expertise of scientists and researchers who guide the discovery and refinement of potential drug candidates, using a combination of *in vitro, in vivo*, and clinical studies. As promising drug candidates are evaluated, the process often requires iterative cycles of testing, refinement, and optimization, which can be costly and time-consuming [42]. The advent of AI technologies, particularly large language models (LLMs) and generative AI, is beginning to significantly reshape this traditional framework. These AI-driven approaches bring advanced computational power and sophisticated algorithms that can rapidly analyze vast amounts of data, enabling researchers to identify patterns, predict outcomes, and optimize drug development more efficiently than ever before [43]. By automating certain aspects of the research process, AI has the potential to speed up the discovery phase, allowing scientists to test hypotheses more quickly and with greater precision. The integration of AI-driven methodologies into the drug development pipeline also promises to enhance effectiveness. AI can be used to predict potential side effects, optimize dosing regimens, and personalize treatment strategies based on patient-specific data [44]. This data-driven approach holds the potential to make drug development not only faster but also more tailored to individual patient needs, which is critical for advancing personalized medicine [45].

3.1. Virtual screening of compounds using AI

Drug screening is a pivotal stage in drug discovery and design, focused on identifying molecules that can interact with therapeutic biomolecules to produce the desired biological response. This process is costly, with expenses reaching billions of dollars. Despite significant investments of time and money, only a small proportion of the screened molecules make it to clinical trials and eventual approval. The incorporation of AI technologies has proven beneficial in enhancing drug screening techniques, offering more cost-effective and time-saving solutions that increase the chances of identifying promising candidates for clinical testing. AI, particularly in the form of virtual screening (VS), has significantly improved high-throughput screening (HTS) methods. AI-powered language models (LMs), which have transformed natural language processing (NLP), have substantially impacted treatment development. In one study, AI-based screening of potential drug molecules achieved an impressive 97% accuracy by simulating drug-target interactions using natural language [46,47]. AI accelerates drug discovery by virtually screening vast libraries of compounds to identify candidates with the highest potential efficacy against HIV (Table 2). Computational models predict binding affinities and assess drug-like properties [48].

Table 1
AI-driven approaches for predicting HIV mutations and resistance patterns.

Study objectives	AI method used	Deductions from study	Ref
Predication of mutation induced HIV-1 reverse transcriptase inhibitor resistance	Multi-drug artificial neural network models	The model exhibited enhanced predictive abilities compared to existing models and can facilitate testing of other mutant isolates of HIV-1 inhibitors	[30]
Genomic analysis and AI for viral mutations prediction and assessment of risks of future pandemics.	Integrated genomic analysis, and AI modelling using machine learning.	Fusion of genomic analysis and AI enhances our ability to mitigate the infectious diseases on a global scale, emphasizing the importance of preventive strategies for protecting public health.	[31].
Prediction of HIV-1 viral mutation because of antiretroviral therapy.	Fully connected neural network combined with graph neural network	The model developed was robust and had great potential for prediction of outcomes from HIV management for informed antiretroviral therapy choices.	[32]
Elucidation of historical knowledge of genotypically determined viral mutation occurrences and viral load measurement on HIV therapy outcomes	Support vector machines (SVM) model for the prediction of HIV therapy outcomes based on the HIV mutation history of the patients.	The study highlighted historical mutations significantly influence therapy prediction, however little the impact. Past treatment and resistance data remain essential in therapy selection.	[33]
To harness high-quality sequence data and ML to study interactions and identify new antiretroviral drug resistance mutations	Machine learning (classifiers)	All mutations directly linked to resistance were identified, and newly discovered drug resistance mutations are accessories. No significant evidence of subtle epistasis involving multiple mutations that, on their own, do not confer resistance.	[34]
To establish a conceptual bridge between natural language and HIV viral evolution	Machine learning algorithms	HIV-1 envelope glycoprotein (HIV Env) viral proteins can accurately predict structural escape patterns using sequence data alone.	[35]
Evaluate the effectiveness of ML architectures for predicting HIV-1 drug resistance using available sequence data and drug resistance assay results	Machine learning (multilayer perception, bidirectional recurrent neural network, and convolutional neural network)	The models revealed the value of interpretability by identifying non-DRM features that may influence genotype-phenotype relationships.	[36]
To assess the predictive ability of the ANN regression models for HIV resistance and mutation	Artificial neural network	The study emphasized the importance of creating and providing access to subtype-specific datasets to enhance the accuracy of drug-resistance prediction methods.	[37]
To develop models that can predict the presence of resistance mutations	ML multilabel classification (MLC) and classifier chains (CC)	By using machine learning, cross-resistance data for reverse transcriptase	[38]
in the RT sequence of HIV		(RT) inhibitors. allowed cross-resistance information in predicting resistance patterns.	
Explore AI methodologies, ML, and deep learning to enhance the prediction of drug resistance mutations in HIV.	ML and deep learning algorithms. Random forests, support vector machines, and neural networks,	AI model can effectively predict HIV drug resistance by analyzing genomic sequences and clinical data.	[39]
Combat HIV drug resistance through the development of predictive models	Genomics and AI techniques	Integration of genomics and AI has the potential to revolutionize HIV treatment and research	[40]
Integration of AI for HIV prevention interventions, aligning with the U. S. goal to end the HIV epidemic within 10 years (announced in 2019)	Combined graph convolutional networks (GCN), an advanced graph-based DL algorithm	AI boosts HIV prevention by improving detection, resource use, and support for vulnerable groups, but adoption challenges must be addressed to impact the achievement of public health goals fully.	[41]

4. AI-driven approaches to novel formulation development for HIV management

Traditional approaches to formulation development often rely on trial-and-error methods and empirical rules, such as the Biopharmaceutics Classification System (BCS). While these approaches provide a foundation, they are constrained by individual expertise, inherent biases, and the time-consuming nature of experimental testing [61]. To overcome these limitations, AI and ML are emerging as transformative tools to streamline formulation optimization [62].

4.1. Linking molecular structure to strategy

AI can revolutionize the formulation development process by identifying correlations between molecular structures and suitable formulation strategies. By analyzing large datasets of marketed drugs, AI models can recognize patterns that inform decisions on solubility enhancement, drug stability, and delivery systems. For instance, classification models can distinguish whether a drug benefits from conventional formulations (e.g., salt formation, particle size reduction) or requires advanced solubilization strategies (e.g., amorphous solid dispersions, lipid-based formulations). AI-driven systems can also optimize excipient selection and predict interactions that influence drug release and stability. For HIV drugs, where adherence is critical, AI can identify formulation strategies that improve patient experience, such as extended-release systems or co-formulation of multiple active ingredients [63].

4.2. AI predictive capabilities in formulation development

The application of ML in drug formulation development began in the 1990s, with neural networks (NNs) being employed to predict the characteristics of immediate-release (IR) oral tablets. These early studies focused on designing and assessing a variety of tablet formulations. The data gathered from these evaluations were subsequently used to train neural networks and decision trees, enabling the prediction of key outcomes such as disintegration time, dissolution rate, and tablet friability [61]. The integration of Artificial Neural Networks (ANNs) into

Table 2
AI-based screening of potential drug molecules for HIV prophylaxis and management.

Methods	Key findings	Lead compound(s)	Mechanism of action	Ref
Support Vector Machine (SVM) model, docking calculations	334 compounds retrieved from virtual screening The SVM model identified seven active compounds. Compounds validated using docking calculations and ADME/Tox parameters, confirming their potential for HIV-1 inhibition.	seven active compounds	Inhibit HIV-1 reverse transcriptase	[49]
Guidance Diffusion for virtual screening (Diff4VS) coupled with graph neural networks such as GAT, GCN, MPNN, Attentive FP.	Diff4VS generates more candidate HIV-inhibiting molecules compared to other methods. 'DrugIndex' a new evaluation method for evolving molecular generative models from a pharmaceutical perspective A new phenomenon, termed Degradation, is observed where generated molecules have a lower similarity to known drug molecules compared to real molecules.	Not specified	The classifier guidance steers the diffusion process to generate molecules that are more similar to known drugs. Ligand-based virtual screening is used to detect HIV-inhibiting candidates from the generated molecules	[50]
ML Predictive Model using molecular descriptors and drug-likeness, Deep Learning re-screening to refine the selection of compounds	1528 compounds initially screened, 41 selected after sequence alignment and machine learning prediction. 22 compounds selected after deep learning rescreening, and 2 compounds highlighted by molecular dynamics simulations.	2 leads [not named]	Potential inhibition of 3CLpro for SARS-CoV-2 management.	[51]
Cyanobacterial secondary metabolite library was screened using ML techniques (message-passing neural networks)	2000 compounds screened. 364 potential antivirals identified, predominantly amides.	Kororamide Mollamide E NostopeptolideA3 Anachelin-H Kasumigamide	Binds to the RNase H active site on HIV-1 RT through non-covalent interactions	[52]
ML integrated with privileged structures (PS) concept	1.5 million compounds screened, 13 unique compounds identified, 2 exhibited antiretroviral effect	Two leads identified	HIV integrase inhibitors	[53]
ML with graph neural network utilizing self-supervised learning	1,824,367 compounds screened, 45 potential non-nucleoside reverse transcriptase inhibitors (NNRTIs) showed potential, 17 known NNRTIs, 28 repurposed moieties with prospects.	2 lead compounds identified	HIV-1 reverse transcriptase inhibitors, specifically targeting wild-type and mutant reverse transcriptase	[54]
ML regression model	4300 traditional compounds screened, 50 compounds potent against HIV, 9 known antiretrovirals.	Dihydroergotamine mesylate	HIV-1 protease inhibitor	[55]
QSAR-based machine learning	37 billion compounds in ZINC-22 screened 124 new anti-HIV drug candidates identified and confirmed. Study underscores the therapeutic potential for further investigations.	124 new anti-HIV drug candidates identified	Inhibits CCR5 protein	[56]
ML computational model	15,235 compounds screened, 8979 integrase inhibitors, 2834 compounds selected for model development, 44 selected from the QSAR model, 3 candidates identified as potential compounds from molecular docking.	PSI-697	HIV integrase inhibitor	[57]
2D and 3D ML-based Quantitative Structure-Activity Relationship	20 compounds, substituted with nitroimidazole moieties, were screened as highly selective and potent inhibitors of non-nucleoside reverse transcriptase (NNRTIs).	Three nitroimidazole analogues identified	Not explicitly stated	[58]
Enchant, by Iambic Therapeutics, uses multimodal transfer learning to predict clinical outcomes from preclinical data, aiding drug discovery.	Enchant excels in predicting human pharmacokinetics (PK), helping to minimize late-stage clinical failures. It surpasses existing models even with limited clinical data, showcasing a breakthrough in drug discovery.	The study generates and predicts multiple candidate molecules without specifying lead compounds.	Enchant utilizes a classifier to direct molecule generation toward drug-like structures. By integrating preclinical and limited clinical data, it accurately predicts key pharmacokinetic properties like half-life.	[59]
'Evo', developed by Stanford University researchers, uses transfer learning model.	Evo enhances genetic sequence processing from around 8000 to over 131,000 base pairs, enabling the creation of new proteins. This advancement supports drug discovery, microbial engineering, and the development of innovative CRISPR-Cas complexes for synthetic biology.	Not specified	Evo utilizes generative AI to study genomes, predict genetic functions, and design novel sequences. By integrating preclinical data, it improves genome analysis and facilitates protein engineering and microbial reprogramming.	[60]

formulation development has revolutionized the field by enabling predictive modeling, optimization, and characterization of pharmaceutical formulations. AI-driven formulation development leverages ANNs to analyze complex datasets, identify key formulation parameters, and predict optimal compositions. Unlike conventional methods, which require numerous experimental iterations, ANNs can process vast amounts of data to determine the most effective formulation strategies. This predictive capability significantly reduces development time and costs while improving formulation efficiency [64].

4.3. ANN-driven optimization of pharmaceutical formulations

ANNs play a crucial role in optimizing pharmaceutical formulations by refining excipient selection, dosage forms, and processing conditions. By utilizing multilayer perception (MLP) models and generalized regression neural networks (GRNNs), researchers can fine-tune formulation parameters to achieve desired drug release profiles, stability, and bioavailability. These models enable precise adjustments, ensuring formulations meet regulatory and therapeutic requirements. AI-driven formulation development also enhances characterization and quality control by predicting dissolution behavior, stability, and shelf-life. ANNs can integrate literature-based data with experimental findings to assess formulation performance under various conditions. This approach minimizes variability and ensures consistency in drug formulations, leading to improved patient outcomes [65].

4.4. Characterization and quality control

AI-driven formulation development is also enhanced by predicting dissolution behavior, stability, and shelf-life. ANNs can integrate literature-based data with experimental findings to assess formulation performance under various conditions. This approach minimizes variability and ensures consistency in drug formulations, leading to improved patient outcomes [63].

Some platforms have also been developed to streamline and optimize drug formulation processes. For instance, Formulation AI represents a groundbreaking innovation as the first freely accessible, web-based platform tailored to revolutionize the design of drug formulations in the pharmaceutical industry [66]. Few researchers have attempted the use of ANN to optimize HIV preventive formulations (Table 3). The dearth of data on the use of AI in formulation development could be attributed to the limitations of this method. While ANN models have shown potential in addressing manufacturing challenges like tablet capping, their application in drug formulation remains underexplored. Unlike process optimization and quality control, drug formulation requires complex multi-parameter modeling (e.g., solubility, stability, and bioavailability), which relies heavily on robust datasets. The limited availability of data in this domain restricts ANN's ability to predict and optimize formulations effectively. Addressing this data gap is essential to harnessing ANN's full potential in revolutionizing pharmaceutical drug formulation processes [67].

5. Discussion and perspectives

5.1. Emerging and less-explored areas in AI predictive modeling

New trends in AI modelling continue to emerge, often providing solutions to challenges with currently available models. While emerging models offer several merits to prediction accuracy, a thorough understanding of these models is essential. Emerging models present opportunities for further research [71]. One of these areas is causal AI, which moves beyond correlation-based models to understand cause-and-effect relationships. This shift is particularly crucial in fields such as healthcare, finance, and climate science, where decision-making based on mere correlations can be misleading [72].

Few-Shot Learning (FSL) is a machine learning paradigm designed to enable models to generalize effectively when only a limited number of labeled examples are available for a task. Unlike traditional machine learning techniques that rely on large-scale datasets, FSL leverages prior knowledge to make learning feasible. This prior knowledge can take various forms, including meta-learning, transfer learning, or embedding-based approaches. The goal is to bridge the gap between AI and human learning, allowing models to adapt rapidly to new tasks with minimal supervision [73]. Transfer Learning refers to the practice of applying knowledge gained from one task or domain to a different but related task or domain. It is particularly useful when labeled data for the target domain is scarce, as models can leverage representations learned from a well-resourced source domain to improve performance on the target domain. Causal AI is an approach to artificial intelligence that goes beyond statistical correlations and aims to understand cause-and-effect relationships in data. Unlike traditional machine learning models that rely on patterns and associations, causal AI uses causal inference techniques to identify the underlying mechanisms driving observed phenomena, making it more interpretable and robust for decision-making [73].

Few-shot and zero-shot learning have gained attention as traditional AI models require vast amounts of labeled data. These techniques aim to make accurate predictions with minimal training examples, which are particularly valuable in rare disease diagnosis and other low-data scenarios [74]. Multimodal AI, which integrates diverse data sources such as text, images, time-series, and molecular structures, is still in its early stages but has the potential to enhance predictive accuracy, particularly in biomedical and pharmaceutical research [75]. Self-supervised learning is another promising direction, reducing dependence on labeled data by leveraging patterns within the data itself. This is particularly useful in fields such as drug discovery and genomics, where obtaining annotated datasets is expensive and time-consuming. AI is also being developed to predict human-computer interactions by understanding user behavior, emotions, and intentions to enhance user experience and develop adaptive AI systems [76]. Quantum computing presents another avenue for AI predictive modeling, with the potential to revolutionize complex system modeling, materials science, and cryptography, although it remains in its infancy [77].

Edge AI, which involves running models directly on edge devices such as smartphones and devices, is becoming increasingly relevant for real-time, low-latency predictions without relying on cloud infrastructure. This has applications in smart healthcare, autonomous vehicles, and industrial monitoring [78].

5.2. Ethical considerations: bias, privacy, and inequality in AI-driven HIV care

As AI becomes more integrated into healthcare systems, it brings not only exciting opportunities but also serious ethical questions

Table 3
AI-driven approaches to novel formulation development for HIV prophylaxis.

Formulation type	AI/ANN method used	Optimization goals	Research summary	Ref
Hyaluronic acid/palm oil-based organogel containing maraviroc	Multilayer full feed forward (MFFF) and multilayer normal feed forward (MNFF) networks	Model optimized mucin adsorption and drug flux	Potential application in vaginal delivery of anti-HIV microbicides, paving the way for further HIV prevention studies.	[68]
Vaginal microbicide delivery of dapivirine (DPV) via a ring or film.	Mechanistic modelling approach using Physiologically Based Pharmacokinetic (PBPK) modelling.	To predict vaginal and cervical drug levels for improved HIV prevention.	The PBPK model successfully predicted pharmacokinetic profiles and area under the curve that matched clinical data.	[69]
Spectrophotometric analysis for Emtricitabine and Tenofovir alafenamide fumarate (TAF) in HIV drugs	ANN with feed-forward back-propagation (Levenberg-Marquardt (LM) and gradient descent with momentum (GDX) algorithms; PLS and PCR models were also used.	To develop a reliable and efficient alternative to HPLC for simultaneous drug quantification.	ANN with LM algorithm showed better performance than GDX; PLS worked better than PCR; no significant difference between ANN and reference HPLC method (ANOVA at 95% CI).	[70]

particularly around fairness, data privacy, and the risk of deepening existing health inequalities. These concerns are especially important in HIV care, where vulnerable populations are already at risk of being underserved.

A recent review by Botha et al. draws attention to how bias can show up in AI tools. These systems learn from data, but if that data reflects existing inequalities or excludes certain groups, the results can be skewed. For example, AI trained mostly on data from urban hospitals may not perform well in rural settings. In HIV care, this could mean missing key risks among groups like young women, people who inject drugs, or men who have sex with men. The review also warns that bias in algorithms can reinforce harmful stereotypes, especially if the systems are not transparent or properly monitored. Privacy is another major concern. AI relies on huge amounts of health data, but there are often gaps in how consent is handled or how securely data is stored. In many cases, patients are unaware of how their information is being used. Botha et al. emphasize the risks of AI systems becoming "black boxes," where even health professionals don't fully understand how decisions are made. This can erode trust and make it harder for patients to have control over their care. There's also the issue of access. AI tools often require strong digital infrastructure and skilled staff, resources that many low- and middle-income countries (where HIV is most common) don't always have. Without intentional efforts to make these tools widely available, they could end up benefiting only a small number of people, while others are left behind. The cost of AI implementation, combined with limited insurance coverage, could make it even harder for under-resourced clinics to catch up [79].

To move forward responsibly, we need to build systems that are inclusive and fair from the start. This includes using diverse datasets, testing models across different settings, and making AI tools transparent and explainable. Ethical guidelines and data protection policies are also essential to protect patients and ensure that AI helps close, rather than widen, the gaps in HIV care [79].

5.3. Future directions

5.3.1. Addressing challenges with AI deployment in HIV research

The future of AI deployment in HIV research holds immense promise, but addressing current challenges is key to unlocking its full potential in HIV research innovation and collaboration. One of the foundational needs is ensuring access to high-quality, diverse, and representative datasets to train robust AI models. Small, non-diverse, or biased datasets can undermine the generalizability and reliability of AI models, especially when applied across different populations or geographies. Data augmentation by synthetic data generation, imputation, and bias correction is essential for enhanced model robustness. Integrating multiple data representations and neural network architectures by collaboration between pharmaceutical companies, regulatory bodies, and research institutes is also essential [19]. Additionally, applying bias correction methods and using advanced oversampling techniques like SMOTE can help balance underrepresented classes within datasets. Collaborative global data-sharing platforms will be essential. This will maintain rigorous privacy and ethical standards to overcome limitations in existing data sources. By integrating data from diverse sources including pharmaceutical companies, research institutions, bioengineering and bioinformatics agencies, and regulatory bodies, AI models are better equipped to capture the intricate patterns and complexities of the HIV epidemic [80]. For example, Bioinformatics tools process viral sequence data to identify mutations, while AI models predict resistance profiles; pharmacologists interpret these predictions to recommend alternative regimens or drug combinations. Also, while Pharmacologists define target drug properties and clinical requirements, AI engineers use machine learning to predict optimal excipient ratios and release profiles; bioinformatics contributes physicochemical and biological data to inform these predictions. Also, in molecular docking studies, bioinformatics identifies potential binding sites using protein structure databases, AI models screen compound libraries for binding affinity and pharmacologists assess the biological relevance of candidate molecules [80].

In parallel, developing explainable AI models will be crucial for building trust and usability among researchers and clinicians. Providing clear insights into the decision-making processes of AI systems will allow end-users to better understand, validate, and interpret the outputs. This transparency will be key for integrating AI tools seamlessly into existing healthcare and research infrastructures [20] Also, translation of AI models trained in a controlled environment to real-world processes ensures poor generalization of the AI model. The use of advanced transfer learning, meta learning, as well as domain adaptation might enhance the translation [81].

As AI-powered solutions are implemented, careful attention must be paid to addressing potential biases, ensuring ethical deployment, and personalizing approaches. Bias identification and mitigation strategies should be developed to eliminate confident AI predictions in uncertain conditions. Probabilistic modeling, Bayesian interference can help improve prediction confidence [82]. Challenges with ethical guidelines on AI deployment in the sensitive healthcare sector can be overcome by human-AI integration or collaboration. The application of human-in-the-loop approach may help create hybrid models that leverage human intuition and machine learning capabilities to enhance prediction accuracy, eliminating ethical concerns. Also, anomaly detection mechanisms that guarantee the security and reliability of predictive models are essential to minimize erroneous predictions due to model data perturbations [83].

AI tools should be designed with user-friendly interfaces and seamless compatibility with existing technologies. By adapting to individual needs, such as predicting drug resistance or tailoring therapies, these solutions can have a profound impact on HIV prevention, testing, and treatment adherence. Ultimately, realizing the full promise of AI in HIV research will require strong multi-stakeholder partnerships. Collaborations between technology companies, researchers, clinicians, and community organizations will be essential for accelerating innovation and ensuring equitable access to these transformative tools. Moreover, implementing adaptive AI systems that can evolve alongside the changing landscape of the HIV epidemic will be crucial for maintaining the relevance and effectiveness of these solutions over time. With a focus on high-quality data, explainable models, and integrated healthcare systems, the future of AI in HIV research holds immense promise for advancing scientific discovery, improving clinical outcomes, and ultimately, ending the HIV epidemic.

5.3.2. Addressing challenges with AI-driven approaches to novel formulation development

Challenges with the solubilization of incorporated moieties can be solved by using AI models based on molecular descriptors that can guide the selection of excipients and techniques to enhance drug solubility and dissolution rates. Moreover, prediction of physiological conditions that are crucial for enhanced bioavailability (for instance, use of enzymes or acidic environment) can be carried out using artificial neural network-driven recommendations, hence accelerating drug formulation development. AI-driven formulation optimization holds immense potential for advancing HIV management. By integrating structural, pharmacological, and clinical data, AI can provide a comprehensive framework for rational formulation design. This approach ensures that HIV drugs not only meet therapeutic targets but also address practical challenges such as patient adherence and manufacturing scalability. This can translate to more effective therapies, improved patient outcomes, and a significant reduction in the global burden of HIV.

The development of advanced predictive modeling capabilities and more sophisticated models that accurately forecast formulation outcomes, such as stability, bioavailability, and release profiles, could integrate multi-scale data, combining molecular, mesoscale, and macroscopic insights to provide a comprehensive understanding of

formulation behavior. Such predictive tools would not only accelerate the development process but also reduce the reliance on costly and time-consuming experimental trials.

The concept of personalized formulations is also gaining traction as a future direction. By harnessing AI, researchers can design patient-specific formulations tailored to individual genetic, metabolic, and physiological profiles. This personalized approach could lead to the development of medicines that are more effective and have fewer side effects, ultimately improving therapeutic outcomes and patient satisfaction.

Real-time process optimization that utilizes AI can make a substantial impact. AI-driven systems can be implemented to monitor and optimize manufacturing processes in real time, ensuring consistent quality and scalability of novel formulations. This capability is particularly valuable in addressing the challenges of large-scale production, where maintaining uniformity and efficiency is critical. The integration of genomics, proteomics, and metabolomics with AI appears promising. By combining these diverse datasets, researchers can uncover novel formulation strategies that target specific biological pathways or mechanisms leading to the development of more effective and targeted therapies, particularly for HIV prophylaxis and management.

AI-enhanced drug-device combinations are also emerging. AI can be used to design and optimize smart drug delivery systems that respond to physiological cues or environmental triggers. These advanced systems could revolutionize the way medications are administered, improving efficacy and patient compliance. Also, Sustainability-driven formulation design is another critical direction for the future. AI can play a pivotal role in developing eco-friendly formulations by optimizing the use of sustainable materials, reducing waste, and minimizing environmental impact throughout the product lifecycle. This approach aligns with the growing demand for environmentally responsible practices in the pharmaceutical and materials science industries.

5.3.3. Prioritization of future AI research directions

The integration of AI into pharmaceutical research is rapidly transforming how drug formulations are developed, tested, and optimized. In the short term, key priorities must focus on maximizing AI's utility in formulation science by ensuring, ethical standards, and regulatory alignment. These priorities include optimizing economic and development efficiencies, establishing ethical guidelines for AI in healthcare innovation, and ensuring model reliability and reproducibility.

Medium-term priorities in AI-driven formulation development should focus on ensuring the scalability, reliability, and ethical use of AI systems. This requires strong interdisciplinary collaboration among formulation scientists, data experts, and regulators to move beyond experimental models and develop robust, generalizable tools that support real-world decision-making. A key challenge is validating complex AI models such as deep learning and generative networks across diverse drug formulation scenarios. These models must be trained on high-quality, representative data and designed to provide interpretable, scientifically sound predictions. Explainability is essential to foster trust and allow formulation scientists to understand and evaluate model outputs. With increasing reliance on AI platforms, ensuring cybersecurity is also critical. Risks such as data breaches and model manipulation could compromise intellectual property and regulatory compliance. As such, secure data handling and digital safety protocols must be built into AI tools used in pharmaceutical contexts. Finally, effective human-AI collaboration is vital. AI should augment, not replace, the expertise of formulation scientists. Tools must be transparent, interactive, and responsive to expert feedback, with regulatory frameworks ensuring human oversight remains central in formulation decisions.

long-term priorities in formulation science must focus on value alignment, control, and governance to ensure AI remains a force for responsible pharmaceutical innovation. Value alignment involves ensuring AI systems used in formulation uphold human values such as safety, efficacy, and equity. As AI begins generating novel drug combinations or delivery strategies, ethical constraints must be embedded to prevent unintended outcomes. AI control and safety are critical as systems gain autonomy in decision-making, such as in adaptive manufacturing or personalized formulations. Transparent oversight, override mechanisms, and safety protocols will be essential to maintain regulatory compliance and trust. Finally, governance of superintelligent AI will require international cooperation to establish theoretical frameworks and ethical boundaries. Anticipating these challenges now is key to safely guiding the future of AI-driven drug development.

6. Conclusions

AI is transforming HIV treatment and prevention by predicting viral mutations and optimizing drug design. AI models analyze molecular descriptors to forecast mutation patterns and guide the development of more effective and resistant drugs. Machine learning algorithms such as logistic regression, support vector machines, random forests, deep neural networks, artificial neural network, recurrent neural networks, convoluted neural networks, and generative models are increasingly used across pharmaceutical research, enabling accurate mutation prediction from genetic sequences, accelerating drug discovery through target-ligand interaction modeling and novel molecule generation, and optimizing formulation development by predicting excipient compatibility, drug release profiles, and stability, ultimately enhancing efficiency and precision across the drug development pipeline. By leveraging AI-driven insights, HIV management can become more personalized, efficient, and sustainable, ultimately reducing global transmission and improving patient outcomes.

CRediT authorship contribution statement

Karamot O. Oyediran: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Peace-Ofonabasi O. Bassey:** Writing – review & editing. **Deborah A. Ogundemuren:** Writing – review & editing. **Abdullahi Abdulraheem:** Writing – review & editing. **Chukwuemeka P. Azubuike:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Andrew N. Amenaghawon:** Writing – review & editing, Methodology, Conceptualization. **Margaret O. Ilomunaya:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Ethics approval and consent to participate

Not applicable.

Availability of data and material

The datasets used during the current study are available from the corresponding author on request.

Declaration of generative AI in scientific writing

The authors acknowledge the use of ChatGPT to summarize certain sentences. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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