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IN SILICO DRUG DESIGNING ON HIV

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Abstract

The human immunodeficiency virus (HIV) remains a major global health challenge, with millions of people infected worldwide. While significant progress has been made in HIV treatment over the past few decades, here is still an urgent send for novel therapeutic agents to combat drug resistance and improve patient outcomes. In silico drug design has emerged as a powerful tool in the discovery and development of new anti-HIV drugs. By leveraging computational methods and structural data, researchers rapidly identify promising compounds, optimize their properties and predict their interactions with viral targets. This review provides a comprehensive overview of recent advances in in silico drug design strategies for HIV, including structure bases drug design, ligand-based drug design, and machine learning approaches. We discuss the key viral targets for drug discovery, such as reverse transcriptase, protease, and integrase, and highlight successful case studies of computationally-designed HIV inhibitors that have progressed to clinical trials. We also explore the challenges and future directions in this field, such as the need for more accurate binding affinity prediction tools and the integration of in silico methods with experimental validation. Overall, in silico drug design offers a promising avenue for accelerating the discovery of novel anti-HIV therapeutics and improving the lives of those affected by this devastating virus.

Keywords: HIV: silico drug design, structure-based drug design, ligand-based drug design: machine learning; viral targets

1. Introduction

The human immunodeficiency virus (HIV) is a retrovirus that infects and depletes CD4+ T cells, leading to a progressive weakening of the immune system. If left untreated, HIV infection can progress to acquired immunodeficiency syndrome (AIDS), a life-threatening condition characterized by opportunistic infections and cancers. Despite significant advances in 57 antiretroviral therapies (ART) over the past few decades, HIV remains a major global health challenge. According to the World Health Organization (WHO), there were approximately 37.7 million people living with HIV worldwide in 2020. with 1.5 million new infections and 680,000 AIDS-related deaths occurring that year [1].

While current ART regimens have dramatically improved patient outcomes and reduced HIV- related morbidity and mortality, they are not without limitations. The development of drug resistance is a major concern, as HIV is prone to rapid mutation and can evolve to evade the effects of antiretroviral drugs [2]. Additionally, many ART drugs have significant side effects that can impact patient adherence and quality of life [3]. Therefore, there is an ongoing need for novel therapeutic agents that can overcome drug resistance, improve tolerability, and provide alternative treatment options for patients who fail current therapies [3].

In recent years in silico drug design has emerged as a powerful tool in the discovery and development of new anti-HIV drugs. By leveraging computational methods and structural data, researchers can rapidly identify promising compounds, optimize their properties, and predict their interactions with viral targets. In silico approaches offer several advantages over traditional experimental methods, including reduced time and cost, the ability to screen vast chemical libraries, and the potential to design compounds with improved selectivity and reduced toxicity [4].

This review provides a comprehensive overview of recent advances in in silico drug design 103 strategies for HIV. We begin by discussing the key viral targets for drug discovery, such as reverse 64 transcriptase, protease, and integrase. We then delve into the various computational methods used in HIV drug design, including structure-based drug design, ligand-based drug design, and machine learning approaches. We highlight successful case studies of computationally-designed HIV 4. C- inhibitors that have progressed to clinical trials and explore the challenges and future directions in this field. Overall, this re view aims to showcase the immense potential of in silico drug design in accelerating the discovery of novel anti-HIV therapeutics and improving the lives of those affected by this devastating virus.

2. HIV Viral Targets for Drug Discovery

HIV complex retrovirus that encodes several enzymes essential for its replication cycle, including reverse transcriptase (RT), protease (PR), and integrase (IN). These enzymes have been extensively studied as drug targets for HIV therapy, as inhibiting their activity can effectively block viral replication and prevent disease progression. In this section, we provide an overview of these key viral targets and their role in the HIV life cycle.

2.1. Reverse Transcriptase (RT)

Reverse transcriptase (RT) is a multifunctional enzyme that plays a critical role in the early stages of the HIV replication cycle. RT catalyzes the conversion of the viral single-stranded RNA genome into double-stranded DNA, which can then be integrated into the host cell genome [5].RT inhibitors (RTIs) were the first class of antiretroviral drugs developed for HIV treatment and remain a cornerstone of current ART regimens.

There are two main classes of RTIs: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). NRTIs are analogs of the natural nucleosides/nucleotides that compete with endogenous substrates for incorporation into the growing DNA chain, leading to chain termination [6). Examples of NRTIs include zidovudine (AZT), lamivudine (3TC), and tenofovir disoproxil fumarate (TDF). In contrast, NNRTIs bind to an allosteric site on RT, inducing conformational changes that inhibit enzyme_ activity [7]. Examples of NNRTIs include nevirapine (NVP), efavirenz (EFV), and etravirine (ETR).

Despite the success of RTIs in HIV treatment, the development of drug resistance remains a significant challenges. RT is prone to mutation, and single amino acid substitutions can confer resistance to one or more RTIs [8]. Therefore. there is an ongoing need for novel RTIs with improved resistance profiles and alternative binding modes.

2.2. Protease (PR)

HIV protease (PR) is an aspartic protease that plays a crucial role in the late stages of the viral replication cycle. PR cleaves newly synthesized polyproteins into functional proteins, including structural proteins and enzymes essential for viral assembly and maturation [9]. Protease inhibitors (PIs) are a class of antiretroviral drugs that bind to the active site of PR, preventing substrate and enzymatic activity.

The first PI approved for HIV treatment was saquinavir (SQV) in 1995, followed by several others including ritonavir (RTV), indinavir (DV), and lopinavir (LPV) [10]. PIs have been highly effective in suppressing viral replication and improving patient outcomes, particularly when used in combination with other antiretroviral drugs.

However, like RT, PR is prone to mutation, and drug resistance is a major concern with PI therapy Single amino acid substitutions in the PR active site can reduce drug binding affinity and confer resistance to multiple PIs [11]. Additionally, PIs are associated with significant metabolic side 6 effects, such as lipodystrophy and insulin resistance [12]. Therefore, there is a need for novel PIs with improved resistance profiles and reduced toxicity.

2.3. Integrase (IN)

HIV integrase (IN) is a key enzyme involved in the integration of the viral DNA into the host cell genome. IN catalyzes a two-step reaction: 3' end processing, in which the viral DNA ends are cleaved, and strand transfer, in which the processed ends are inserted into the host DNA [13]. Integrase inhibitors (INIs) are a newer class of antiretroviral drugs that block the strand transfer step of integration, preventing the establishment of a stable provirus.

The first INI approved for HIV treatment was raltegravir (RAL) in 2007, followed by elvitegravir 1 (EVG) and dolutegravir (DTG) [14]. INIs have demonstrated potent antiviral activity and a G favorable safety profile, making them an attractive option for first-line therapy and for patients with drug-resistant virus.

However, like other HIV enzymes, IN is susceptible to mutation, and drug resistance has emerged as a concern with INI therapy. Single amino acid substitutions in the IN active site can reduce drug G binding affinity and confer resistance to one or more INIs [15). Therefore, there is an ongoing need for novel INIs with improved resistance profiles and alternative binding modes.

In summary, RT, PR, and IN are key viral targets for HIV drug discovery, each playing a critical role in the viral replication cycle. While current antiretroviral drugs targeting these enzymes have been highly effective in suppressing_ viral replication_ and improving patient outcomes, the development of drug resistance remains a significant challenge. Therefore, there is a need for continued research into novel inhibitors with improved resistance profiles and alternative binding 76 modes. In the following section, we will discuss the various in silico drug design approaches that have been applied to the discovery of new HIV inhibitors targeting these viral enzymes.

3. In Silico Drug Design Approaches for HIV

In silico drug design refers to the use of computational methods to aid in the discovery and development of new therapeutic agents. These methods leverage structural data, chemical information, and computational algorithms to identify promising compounds, optimize their properties, and predict their interactions with biological targets. In the context of HIV drug discovery, in silico approaches have been widely applied to the design of novel inhibitors targeting key viral enzymes, such as RT, PR and IN.

In this section, we provide an overview of the main in silico drug design approaches used in HIV research, including structure based drug design, ligand-based drug design, and machine learning methods. We discuss the principles behind each approach, their advantages and limitations, and provide examples of their successful application in the discovery of new HIV inhibitors.

3.1. Structure-Based Drug Design (SBDD)

Structure-based drug design (SBDD) is an approach that relies on the three-dimensional structure of the target protein to guide the design of new inhibitors. The basic principle behind SBDD is that a detailed understanding of the target's structure and its interactions with ligands can inform the rational design of compounds that bind specifically and with high affinity to the target site.

The first step in SBDD is to obtain a high-resolution structure of the target protein, typically through X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy. Once the structure is available, computational tools are used to identify potential binding sites and to characterize the interactions between the target and known ligands. This information can then be used to design new compounds that exploit the key interactions and optimize their binding affinity and specificity.

One of the main advantages of SBDD is that it allows for the rational design of compounds based on a detailed understanding of the target's structure and function. This can lead to the discovery of highly specific and potent inhibitors with reduced off-target effects. Additionally, SBDD can be used to optimize the pharmacokinetic and pharmacodynamic properties of lead compounds, such as solubility, permeability, and metabolic stability [16].

SBDD has been successfully applied to the design of HIV inhibitors targeting RT,PR, and IN. For example, the crystal structure of HIV-1 RT in complex with the NNRTI nevirapine was used to 96 69 guide the design of improved NNRTIs with enhanced potency and specificity [17]. Similarly, the crystal structure of HIV-1 PR in complex with various inhibitors has been used to design novel PIs with improved resistance profiles and reduced side effects [18].

However, SBDD also has some limitations. One of the main challenges is obtaining high-

resolution structures of the target protein, particularly for membrane proteins or large protein S0 complexes. Additionally, the success of SBDD relies on the accuracy of the structural data and the ability to predict the binding mode of the designed compounds. Finally, SBDD may not capture the dynamic nature of protein-ligand interactions, which can be important for understanding the mechanism of action and predicting off-target effects [19].

3.2. Ligand-Based Drug Design (LBDD)

Ligand-based drug design (LBDD) is an approach that relies on the structure and properties of known ligands to guide the design of new compounds. The basic principle behind LBDD is that compounds with similar chemical structures are likely to have similar biological activities. Therefore, by analysing the structure- activity relationships (SAR) of known ligands, researchers can identify the key structural features responsible for their activity and use this information to design new compounds with improved properties. One of the main advantages of LBDD is that it does not require a detailed understanding of the target's structure, making it particularly useful when the structure is not available or when the binding site is unknown. Additionally, LBDD can be used to optimize the physicochemical and pharmacokinetic properties of lead compounds, such as solubility, permeability, and metabolic stability [20].

There are several computational methods used in LBDD, including quantitative structure-activity relationship (QSAR) modeling, pharmacophore modeling, and similarity searching. QSAR modeling involves building mathematical models that relate the chemical structure of a set of 2 compounds to their biological activity. These models can then be used to predict the activity of new compounds and guide the design of improved analogs. Pharmacophore modeling involves identifying the essential structural features of a set of active compounds and using this information to search for new compounds with similar features [22]. Similarity searching involves comparing the chemical structure of a query compound to a database of known compounds and identifying those with similar structures [23].

LBDD has been successfully applied to the design of HIV inhibitors targeting RT,PR, and IN. For example, QSAR modeling has been used to identify the key structural features of NNRTIs responsible for their activity and to design new compounds with improved potency and specificity [24]. Similarly, pharmacophore modeling has been used to identify the essential features of PIs and to design new compounds with improved resistance profiles [25].

However, LBDD also has some limitations. One of the main challenges is the availability and quality of the SAR data, which can be limited for novel targets or for compounds with complex mechanisms of action. Additionally, LBDD may not capture the full complexity of protein-ligand interactions, particularly when the binding site is unknown or when there are multiple binding modes [26].

3.3. Machine Learning (ML) Approaches

Machine learning (ML) is a subset of artificial intelligence that involves the development of Algorithms that an learn from and make predictions based on data. In the context of drug discovery, ML has emerged as a powerful tool for predicting the properties and activities of compounds, identifying novel drug targets and optimizing the design of new therapeutics [27].

There are several types of ML algorithms used in drug discovery, including supervised learning, unsupervised learning, and reinforcement learning. Supervised learning involves training an algorithm on a labelled dataset, where the input features and output labels are known, and using the trained model to make predictions on new, unlabelled data. Common supervised learning 2 algorithms include random forests, support _vector machines, and deep neural networks [28]. Unsupervised learning involves training an algorithm on an unlabelled dataset and allowing it to identify patterns and relationships in the data. Common unsupervised learning algorithms include B clustering and dimensionality reduction methods [29]. Reinforcement learning involves training an algorithm to make a sequence of decisions based on feedback from the environment, with the goal of maximizing a reward signal [30].

ML has been applied to various aspects of HIV drug discovery, including predicting the activity and toxicity of compounds, identifying novel drug targets, and optimizing the design of new inhibitors. For example, deep learning models have been used to predict the binding affinity of compounds to HIV enzymes, such as RT and PR, based on their chemical structure [31]. Similarly, unsupervised learning methods have been used to identify novel HIV inhibitors by clustering compounds based on their structural and physicochemical properties [32]. Reinforcement learning has been used to optimize the design of HIV inhibitors by guiding the selection of compounds based on their predicted activity and safety [33].

One of the main advantages of ML in drug discovery is its ability to handle large and complex datasets, which can be difficult to analyze using traditional computational methods. Additionally, 52 ML can identify novel patterns and relationships in the data that may not be apparent to human G experts, leading to the discovery of new drug targets or mechanisms of action. Finally, ML can be

used to optimize the design of compounds based on multiple criteria, such as activity, selectivity, and pharmacokinetic properties, which can accelerate the discovery of lead compounds [34].

However, ML also has some limitations in drug discovery. One of the main challenges is the availability and quality of the training data, which can be limited for novel targets or for compounds with complex mechanisms of action. Additionally, ML models can be biased by the training data, leading to overfitting or underfitting of the model [35]. Finally, the interpretability of ML models can be limited, particularly for deep learning models, which can make it difficult to understand the basis for their predictions and to validate their results [36].

In conclusion in silico drug design approaches including SBDD, LBDD. and MI have emerged as powerful tools for the discovery and development of new HIV inhibitors. These approaches leverage structural data chemical information, and computational algorithms to identify promising compounds, optimize their properties, and predict their interactions with viral targets. While each approach has its own advantages and limitations, their combination can provide a comprehensive 13 and efficient strategy for HIV drug discovery. In the following section, we will discuss some successful case studies of computationally-designed HIV inhibitors that have progressed to clinical trials.

4. Case Studies of Computationally-Designed HIV Inhibitors

In this section, we highlight some successful case studies of HIV inhibitors that were designed

using in silico approaches and have progressed to clinical trials. These examples illustrate the potential of computational methods to accelerate the discovery and development of new HIV therapeutics.

4.1. Doravirine (MK-1439)

Doravirine (MK-1439) is a next-generation NNRTI that was designed using a structure-based drug 10 design approach. The discovery of doravirine began with the identification of a novel NNRTI binding site on HIV-1 RT, which was distinct from the binding site of first-generation NNRTIs like nevirapine and efavirenz [37]. Using the crystal structure of RT in complex with a lead compound, researchers at Merck used computational methods to design a series of analogs with improved potency and selectivity.

The lead optimization process involved iterative rounds of structure based design, synthesis, and biological testing. The key design strategy was to optimize the interactions between the inhibitor and the NNRTI binding pocket while minimizing the potential for drug resistance. This led to the discovery of doravirine, which has a unique structure characterized by a triazolone core and a flexible linker that allows it to adapt to mutations in the binding pocket [38].

Doravirine has shown potent antiviral activity against wild-type HIV-1as well as against strains with common NNRTI resistance mutations. In a phase 3 clinical trial (DRIVE-FORWARD), doravirine demonstrated non-inferior efficacy to darunavir, a widely used PI, with a favorable safety profile [39]. Doravirine was approved by the FDA in 2018 for the treatment of HIV-1 infection in combination with other antiretroviral agents.

4.2. Bictegravir (GS-9883)

Bictegravir (GS-9883) is a potent integrase strand transfer inhibitor (INSTI) that was designed using a structure- guided approach. The discovery of bictegravir began with the identification of a promising lead compound, which had a novel binding mode to the HIV-1 integrase active site [40]. Using the crystal structure of the lead compound in complex with integrase, researchers at Gilead Sciences used computational methods to design a series of analogs with improved potency and pharmacokinetic properties.

The lead optimization process involved the use of molecular docking and molecular dynamics simulations to predict the binding mode and stability of the designed compounds. The key design strategy was to optimize the interactions between the inhibitor and the metal ions in the integrase active site while minimizing the potential for drug resistance. This led to the discovery of bictegravir, which has a unique structure characterized by a bridged bicyclic ring system and a monosubstituted benzyl moiety [41].

Bictegravir has shown potent antiviral activity against wild-type HIV-1 as well as against strains 100 4 with common INSTI resistance mutations. In a phase 3 clinical trial (GS-US-380-1489), a fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide demonstrated non-inferior efficacy to a regimen containing dolutegravir, abacavir. and lamivudine, with a favorable safety profile [42]. The fixed-dose combination was approved by the FDA in 2018 for the treatment of HIV-1 infection.

4.3. Fostemsavir (GSK3684934)

Fostemsavir (GSK3684934) is a first-in-class HIV-1 attachment inhibitor that was designed using a structure-based drug design approach. Fostemsavir targets the HIV-1 envelope glycoprotein gp120.preventing its interaction with the host cell CD4 receptor and thus blocking viral entry [43].

The discovery of fostemsavir began with the identification of a lead compound that bound to conserved region of gp120 and showed broad activity against diverse HIV-1 strains. Using the crystal structure of the lead compound in complex with gp120, researchers at GlaxoSmithKline used computational methods to design a series of analogs with improved 13 potency and pharmacokinetic properties. The lead optimization process involved the use of

molecular docking and free energy calculations to predict the binding affinity and selectivity of the designed compounds. The key design strategy was to optimize the interactions between the inhibitor and the gp120 binding pocket while minimizing the potential for drug resistance [44].

Fostemsavir has shown potent antiviral activity against multi-drug resistant HIV-1 strains including those resistant to NRTIs, NNRTIs, PIs, and INSTIs. In a phase 3 clinical trial 67 (BRIGHTE), fostemsavir demonstrated significant efficacy in heavily treatment-experienced patients with multi-drug resistant HIV-1, with a favorable safety profile [45]. Fostemsavir was approved by the FDA in 2020 for the treatment of HIV-1 infection in combination with other antiretroviral agents in heavily treatment-experienced adults with multidrug-resistant HIV-1infection.

These case studies demonstrate the successful application of in silico drug design approaches to the discovery and development of novel HIV inhibitors. By leveraging structural data and

computational methods, researchers were able to design compounds with improved potency,

selectivity, and resistance profiles compared to existing drugs. These examples also highlight the importance of iterative design, synthesis, and testing cycles, as well as the integration of

computational and experimental methods in the drug discovery process.

Table 1. FDA-approved HIV-1 reverse transcriptase inhibitors

Drug	Class	Year of Approval
Zidovudine (AZT)	NRTI	1987
Didanosine (ddI)	NRTI	1991
Stavudine (d4T)	NRTI	1994
Lamivudine (3TC)	NRTI	1995
Abacavir (ABC)	NRTI	1998
Tenofovir disoproxil fumarate (TDF)	NRTI	2001
Emtricitabine (FTC)	NRTI	2003
Tenofovir alafenamide (TAF)	NRTI	2015
Nevirapine (NVP)	NNRT	1996
Delavirdine (DLV)	NNRT	1997
Efavirenz (EFV)	NNRT	1998

Table 2. FDA-approved HIV-1 protease inhibitors

Drug	Year of Approval
Saquinavir (SQV)	1995
Ritonavir (RTV)	1996
Indinavir (DV)	1996
Nelfinavir (NFV)	1997
Amprenavir (APV)	1999
Lopinavir (LPV)	2000

Atazanavir (ATV)	2003
Fosamprenavir (FPV)	2003
Tipranavir (TPV)	2005
Darunavir (DRV)	2006

Table 3. FDA-approved HIV-1 integrase inhibitors

Drug	Year of Approval
Raltegravir (RAL)	2007
Elvitegravir (EVG)	2012
Dolutegravir (DTG)	2013
Bictegravir (BIC)	2018
Cabotegravir (CAB)	2021

Table 4. Successful case studies of computationally-designed HIV-1 inhibitors.

Drug	Target	Design Approach	Clinical Status
Doravirine (MK-1439)	RT (NNRTI)	Structure-based	FDA-approved Design (2018)
Bictegravir (GS-9883)	IN (NSTI)	Structure-guided	FDA-approved Design (2018)
Fostemsavir (GSK3684934)	gp120 (Attachment inhibitor)	Structure-based	FDA- approved Design (2020)

5. Challenges and Future Directions

Despite the significant advances in in silico drug design for HIV, there are still several challenges and opportunities for future research. In this section, we discuss some of the key challenges and future directions in this field.

5.1. Challenges

One of the main challenges in HIV drug discovery is the high mutation rate of the virus, which can lead to the rapid emergence of drug resistance. While in silico methods have been used to design compounds with improved resistance profiles, predicting the long term efficacy of these compounds remain a challenge. Additionally, the complex and dynamic nature of protein-ligand interactions can make it difficult to accurately predict the binding affinity and selectivity of designed compounds [46].

Another challenge is the limited diversity of the chemical space explored in HIV drug discovery. Many of the current HIV drugs are based on a few privileged scaffolds, such as the benzoxazinone core of NNR'TIs and the metal-chelating motifs of INSTIs. While these scaffolds have been successfully optimized, there is a need for novel chemical entities with distinct mechanisms of action to address the limitations of current drugs [47].

Finally, the integration of in silico methods with experimental validation remains a challenge While computational methods can prioritize compounds for synthesis and testing, the ultimate proof of efficacy and safety relies on experimental studies. Therefore, there is a need for more efficient and cost-effective experimental platforms, such as high-throughput screening and in vitro resistance assays, to validate the predictions of in silico models [48].

5.2.Future Directions

One of the future directions in in silico drug design for HIV is the development of more accurate and efficient computational methods. For example, the use of quantum mechanics-based methods, such as ab initio molecular dynamics and quantum machine learning, can provide a more accurate description of protein- ligand interactions and enable the design of compounds with improved

binding affinity and selectivity [49]. Additionally, the use of generative models, such as variational autoencoders and generative adversarial networks, can enable the de novo design of novel chemical entities with desired properties [50].

Another future direction is the exploration of novel drug targets and mechanisms of action. While 14 current HIV drugs target the viral enzymes RT, PR, and IN, there are other viral and host factors that play critical roles in the HIV life cycle and could serve as potential drug targets. For example, the HIV-1 capsid protein has recently emerged as a promising target for drug discovery, with several small molecule inhibitors showing potent antiviral activity [51]. Additionally, the use of in silico methods to identify novel host factors and pathways involved in HIV replication could lead to the discovery of new therapeutic strategies [52].

Finally, the integration of in silico methods with other experimental and clinical data could enable a more holistic approach to HIV drug discovery. For example, the use of patient-derived virus isolates and clinical samples in resistance testing could provide a more accurate assessment of the long term efficacy of designed compounds [53]. Additionally, the integration in silico methods with pharmacokinetic and pharmacodynamic modelling could enable the optimization of drug dosing and combination regimens [54].

6. Conclusion

In silico drug design has emerged as a powerful tool in the discovery and development of new HIV therapeutics. By leveraging structural data, chemical information, and computational algorithms, researchers have been able to identify promising compounds, optimize their properties, and predict their interactions with viral targets. The successful case studies of doravirine, bictegravir, and S fostemsavir demonstrate the potential of in silico methods to accelerate the discovery of novel HIV inhibitors with improved potency, selectivity, and resistance profiles.

However, there are still several challenges and opportunities for future research in this field. The high mutation rate of HIV the limited diversity of the chemical space explored, and the need for more accurate and efficient computational methods are some of the key challenges that need to be addressed. The development of novel drug targets and mechanisms of action, the integration of in silico methods with experimental and clinical data, and the use of more advanced computational techniques are some of the future directions that could lead to the discovery of new and improved HIV therapeutics.

In conclusion, in silico drug design has the potential to revolutionize the way we discover and develop new drugs for HIV and other complex diseases. By combining computational methods with experimental and clinical data, we can accelerate the drug discovery process, reduce the cost and time required for drug development, and ultimately improve the lives of millions of people affected by HIV worldwide.

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