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An In silico Based Comparison of Drug Interactions in Wild and Mutant Human HIV-1 RT through Docking Studies

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Abstract

Introduction:

The aim of this research is to compare the drug interactions between wild-type and mutant forms of human HIV-1 reverse transcriptase (RT) using in silico docking studies

Materials and methods:

Extract the crystal structures of wild-type HIV-1 RT (PDB ID: 6CQJ) and K103N/Y181C mutant RT (PDB ID: 6COR) from Protein Data Bank, antiviral drugs were downloaded from Pubchem server. Docking was carried out by HEX docking server and interaction was analyzed using Docking energy.

Discussion:

The findings of this research could contribute to the development of more effective antiretroviral therapies tailored to specific mutations and aid in the design of novel drugs targeting drug-resistant HIV-1 strains. Ultimately, this research may contribute to improving the treatment outcomes and quality of life for individuals living with HIV-1 infection.

Conclusion:

From the analysis the drug of Zidovudine has shown in Wild type Structure whereas Didanosine the drug which was shown in highest interaction of Mutant type structure.

Keywords:

Introduction:

HIV specifically targets the immune system, notably CD4 cells, crucial for defending against infections. Without treatment, HIV can progress to AIDS, a condition where the immune system is severely compromised(1). HIV spreads through contact with infected bodily fluids, including semen, vaginal fluids, and blood. Common transmission routes include unprotected sex, sharing needles, and mother-to-child transmission during childbirth or breastfeeding (2). Upon entering the body, HIV attacks and kills CD4 cells, weakening the immune system, this makes the person susceptible to infections and certain cancers. The progression from HIV to AIDS may not exhibit symptoms initially, but the virus can still be transmitted (3). Antiretroviral therapy (ART) inhibits viral replication, transforming HIV into a chronic, manageable condition, although a cure remains elusive (4). Antiretroviral drugs (ARVs) are essential medications designed to combat infections caused by retroviruses, with HIV (Human Immunodeficiency Virus) being the most widely recognized among them. The primary mechanism of ARVs involves impeding the virus's replication, thereby decelerating the advancement of HIV infection and effectively managing its associated symptoms. These drugs have played a pivotal role in transforming HIV from a once fatal illness into a manageable chronic condition (5,6).

Consistent adherence to the prescribed ARV regimen is of paramount importance for individuals living with HIV. When taken as directed, ARVs play a significant role in suppressing the viral load, enhancing the immune system, and retarding the progression of HIV infection. Conversely, discontinuation of treatment or non-adherence to the prescribed regimen can lead to the development of drug resistance and eventual treatment failure. Routine monitoring of viral load and CD4 cell counts is crucial for healthcare providers to evaluate treatment effectiveness and make necessary adjustments as required (5).

Preventative measures, such as pre-exposure prophylaxis (PrEP), needle exchange programs, and safe sex practices, play a crucial role in reducing HIV transmission. Public awareness, education, and destigmatization are essential in the global fight against HIV (7). Despite advancements, drug resistance in HIV-1 RT poses a challenge to antiretroviral treatments. Understanding the molecular mechanisms of drug resistance is vital for developing innovative and durable therapies (8).

Didanosine, also referred to as ddI, operates as a nucleoside reverse transcriptase inhibitor (NRTI), hindering the function of reverse transcriptase, an essential enzyme for the replication of the HIV virus. Its mechanism involves integration into the developing viral DNA chain, leading to premature termination and the inhibition of further viral replication(9). Frequently, didanosine

is administered in conjunction with other antiretroviral drugs to increase the effectiveness and decrease the risk of drug resistance. Although didanosine has proven efficacy in suppressing viral replication, it is crucial to acknowledge potential side effects, encompassing gastrointestinal symptoms like nausea, diarrhea, and pancreatitis(10) . Vigilant monitoring and precise dosing are imperative to address these side effects and optimize the outcomes of treatment.

Zidovudine (AZT), another notable antiretroviral drug, belongs to the NRTI class as well. It also functions by hindering reverse transcriptase, preventing the conversion of viral RNA into DNA. Zidovudine emerged as one of the pioneering antiretroviral drugs approved for HIV treatment, playing a pivotal role in the initial phases of the epidemic(11) . Despite its effectiveness, zidovudine is linked to side effects such as anemia, neutropenia, and hematological toxicity(12). Zidovudine is commonly incorporated into combination therapy, contributing to the comprehensive suppression of viral replication. The use of a combination therapy involving didanosine and zidovudine has been shown to effectively slow down the progression of disease and extend the lifespan of individuals with intermediate or advanced HIV infection.This has been observed in both previously untreated individuals and those with prior experience with antiretroviral therapy, emphasizing its efficacy in managing intermediate or advanced stages of HIV infection(13).

This study employs computational techniques, specifically molecular docking simulations, to explore interactions between antiretroviral drugs and wild-type and mutant forms of HIV-1 RT. The focus is on predicting binding affinities and interaction modes, providing insights into structural alterations in mutant HIV-1 RT. By comparing wild-type and mutant structures, potential changes in drug binding sites and affinities can be identified. This in silico investigation complements experimental studies, offering a cost-effective means to explore diverse drug interactions. The findings may inform the design of more robust antiretroviral therapies against drug-resistant HIV-1 strains, contributing to efforts in addressing evolving drug resistance in HIV-1.

Materials and method:

Extraction of crystal structures

To extract The crystal structures of wild-type HIV-1 RT (PDB ID: 6C0J) and K103N/Y181C mutant RT (PDB ID: 6C0R) of from Protein Data Bank

Antiviral drugs were downloaded from Pubchem server. Docking was carried out by HEX docking server. Interaction was analyzed using Docking energy.

Screening of docked molecules was performed based on highest binding energy. Docking of target enzyme-substrate was performed to determine the binding energy of interaction and analysis of the docking result was carried out for identification of potential inhibitor.

Two-dimensional chemical structures in structured data format (SDF) were retrieved from PubChem-NCBI database and SDF format was converted into Protein data bank (PDB) format through OpenBabel 2.3.1 version. The three dimensional structure of protein structures was obtained from Protein Data Bank.

The receptor crystallographic water molecules were removed from the protein. The retrieved Drugs were individually using Hex 8.0.0. Protein docking program (http://hex.loria.fr), the Hex server is the first Fourier Transform (FFT) based analytics. In this method, rigid docking is undertaken taking into consideration different orientations through 6D analysis. The HEX program carries out a complete search over all six rigid-body degrees of freedom by rotating and translating the expansion coefficients.

This was carried out by maintaining suitable parameters such as FFT mode-3D fast lite, grid dimension-0.6, receptor range-180, ligand range-180, twist range-360 and distance range-40. Docked complexes of protein and ligand interaction were visualized in Pymol.In the Hex Docking server 8.0 versions, more negative E-total value implied that there exists a strong interaction between ligand and receptor and that leads to activation of receptor activity.

Result:

In Figure.1 the wild type HIV-1 RT is the unaltered, naturally occurring strain of the virus. Wild-type HIV can acquire mutations that render it resistant to particular HIV medications when exposed to antiretroviral medications.

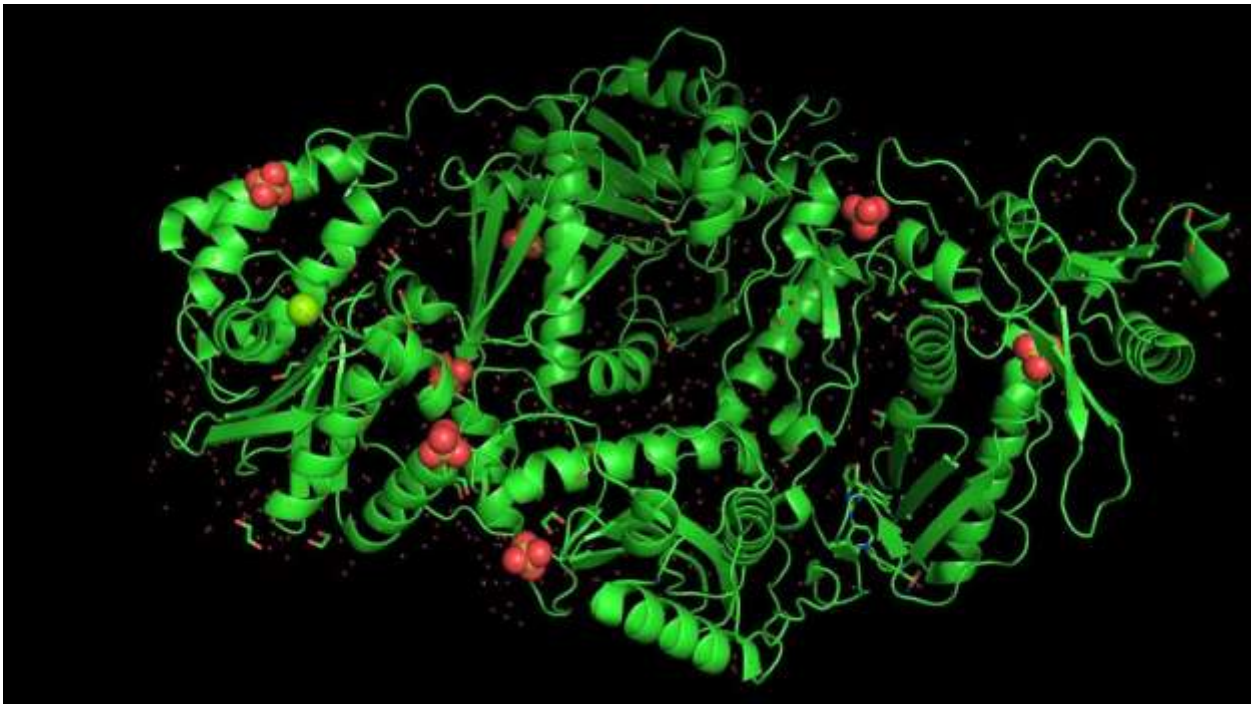

Figure. 1 The crystal structures of wild-type HIV-1 RT (PDB ID: 6C0J)

Figure. 2 shows K103N and Y181C which are the most frequent mutations linked to Nevirapine resistance among NNRTI drug mutations. Low frequencies of K103N and Y181C are substantially linked to an elevated risk of virologic failure, even in patients who were not on antiretroviral therapy (ART).

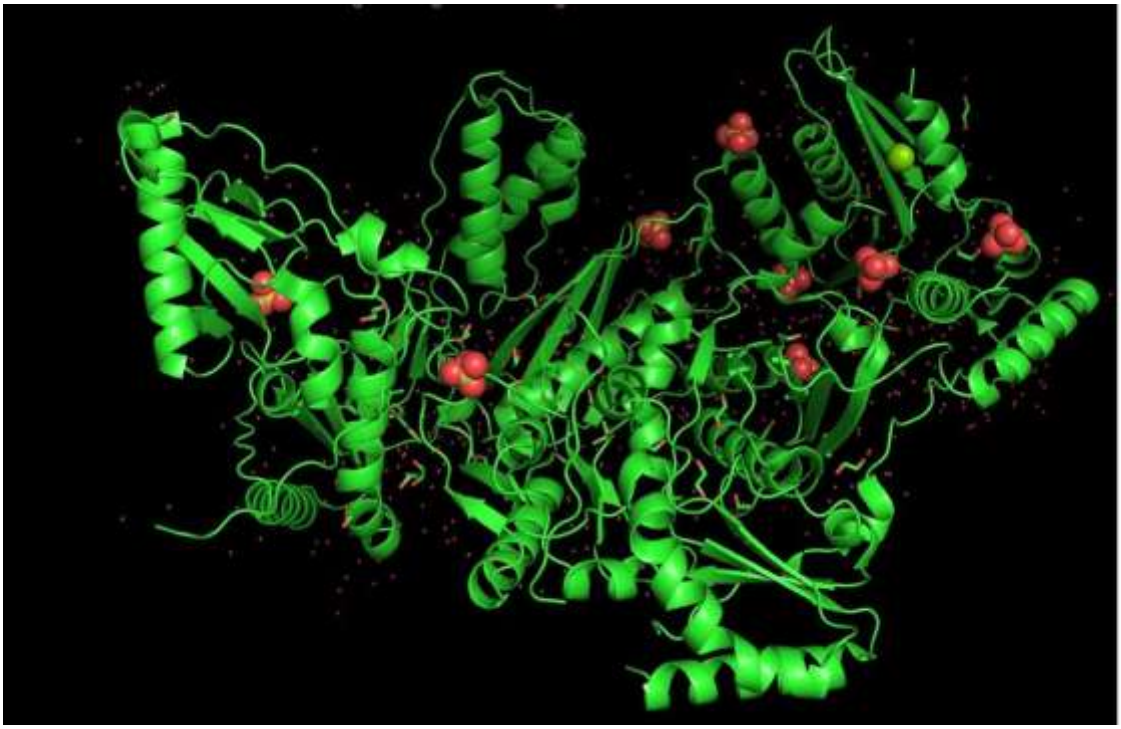

Figure. 2 The crystal structures of K103N/Y181C mutant RT (PDB ID: 6C0R)

In Figure.3 the crystallography of the wild-type HIV-1 RT (PDB ID: 6C0J) K103N/Y181C mutant RT (PDB ID: 6C0R) are superimposed for further docking interactions with drugs.

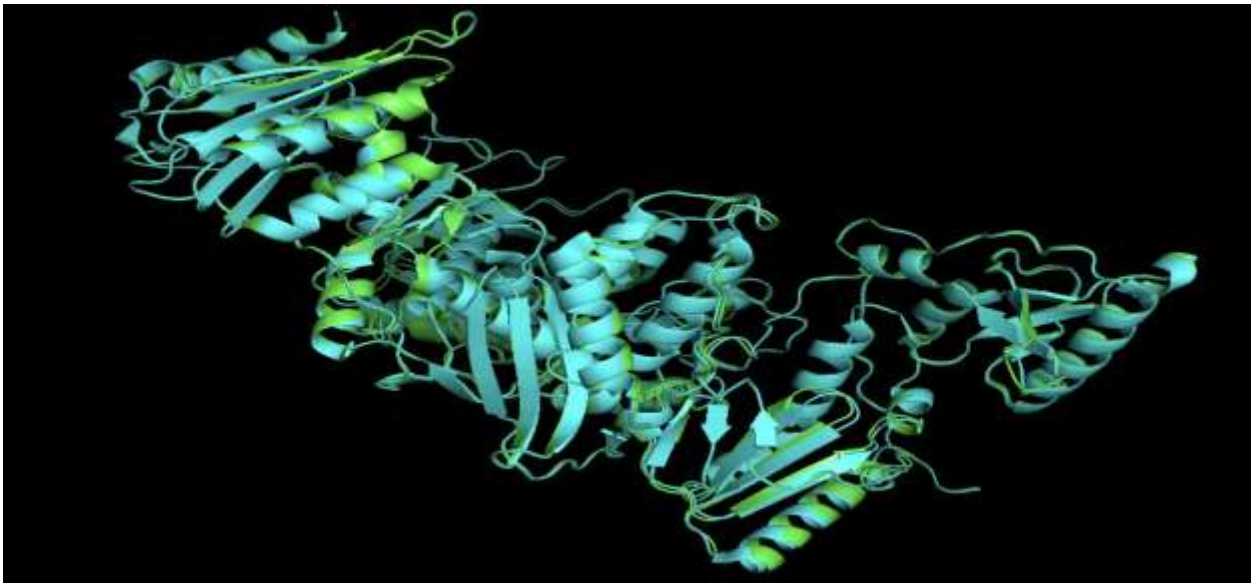

Figure. 3 Superimposed structure between 6C0J and 6C0R

The table below shows the drug interactions of 7 drugs with wild type and mutant type HIV, the drugs are Lamivudine, Emtricitabine, Tenofovir, Abacavir, Zidovudine, Didanosine and Stavudine. Amongst all the drug interactions with the crystal structures, Zidovudine had the highest docking score with the wild type HIV-1 RT and Didanosine had the highest docking score with the Mutant HIV RT amongst the 7 drugs chosen

Table 1 Interactions between the antiviral drugs and crystal structures of wild-type HIV-1 RT (PDB ID: 6C0J) and K103N/Y181C mutant RT (PDB ID: 6C0R)

PubChem CID	Drug	Wild type	Mutant type
60825	Lamivudine	-212.26	-205
60877	Emtricitabine	-244.41	-239.22
464205	Tenofovir	-197.73	-195.56
441300	Abacavir	-202.22	-210.21
35370	Zidovudine	**-264.22**	-256.04
135398739	Didanosine	-235.42	**-276.83**
18283	Stavudine	-235.42	-228.64

By understanding the crystallographic structure of viral proteins, researchers can create drugs that are less likely to cause resistance. Drugs that target structurally significant areas or conserved regions can be designed to have a longer-lasting effect on viral propagation.

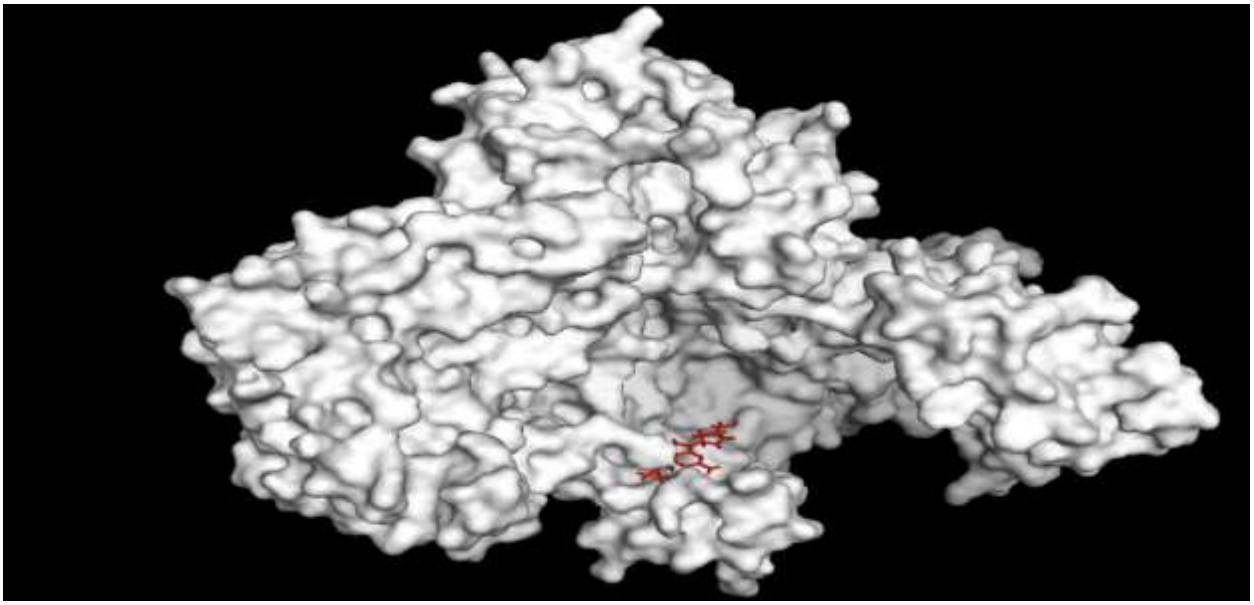

Figure.4 Wild type interaction with Zidovudine

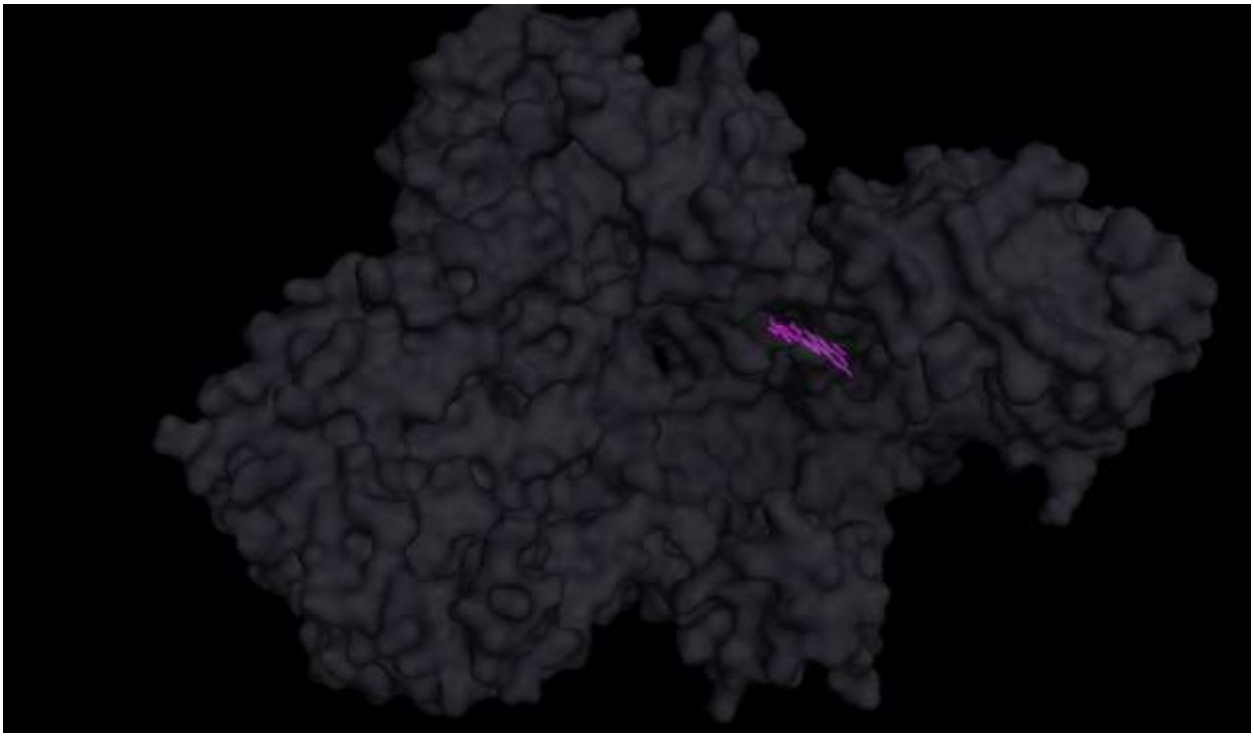

Figure.5 Mutant type interaction with Didanosine

Drug interaction sites on viral proteins are identified with the use of crystallography. Through comprehension of the binding mechanisms of drugs to these locations, researchers can refine drug compounds to improve both therapeutic efficacy and binding affinity. Drug resistance in viruses can develop over time. By understanding the crystallographic structure of viral proteins, researchers can create drugs that are less likely to cause resistance. Drugs that target structurally significant areas or conserved regions can be designed to have a longer-lasting effect on viral propagation.

Discussion

The observed variations in the docking scores between didanosine and zidovudine with the wild-type and mutant HIV-1 RT structures provide important information about possible antiretroviral treatment implications(14). Zidovudine's higher docking score with the wild-type structure indicates a strong and favorable binding affinity. This result is consistent with zidovudine's past efficacy as a first-line antiretroviral medication. Zidovudine may remain a reliable part of antiretroviral therapy for individuals with wild-type HIV-1 infection, based on its interaction with the wild-type RT structure(15).

On the other hand, the highest interaction between didanosine and the mutant-type structure indicates a significant change in drug binding. In comparison to other medications under investigation, didanosine binding appears to be more favored by the mutant-type HIV-1 RT

structure, which is influenced by particular mutations. This finding causes concern because didanosine may be more effective against some virus mutant strains, which could lead to the development of resistance. Didanosine's increased interaction with the mutant structure indicates the need for extra caution in the face of emerging drug-resistant viral variants, while zidovudine's continued efficacy against the wild-type structure reaffirms its role in antiretroviral therapy (16). The results of the study have consequences for the creation of drugs and clinical practice. When choosing antiretroviral drugs for patients, doctors may need to take into account the unique genetic makeup of the patient's HIV-1 strain, particularly if mutations linked to didanosine resistance are common(17).

Moreover, pharmaceutical companies may use this data to create next-generation antiretrovirals that work against a variety of viral strains, including ones with mutations linked to resistance. Although in silico studies yield useful predictions, in vitro and in vivo experiments are necessary to confirm these results. The study also emphasizes how crucial it is to continuously monitor HIV-1's genome in order to identify new mutations and modify treatment plans as necessary. The results of this study may help design new medications that target drug-resistant HIV-1 strains and aid in the development of more potent antiretroviral therapies based on particular mutations. Ultimately, this study could help those with HIV-1 infection live better lives and receive better treatment outcomes.(18,19) (20,21)

Conclusion

From the analysis the drug of Zidovudine has shown the highest docking score with Wild type Structure whereas Didanosine the drug was shown in highest interaction with Mutant type structure.

Conflict of Interest:

The author reported the conflict of interest while performing this study to be nil.

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