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# Targets for Anti-HIV1- Agents as Personalized HIV Therapy: a Review Study

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Abstract:

The enormous genetic variety of the viral population harbored by the patient and the large volume of therapeutic alternatives characterize HIV therapy. Each patient and period has its viral population. The enormous number of therapy possibilities makes selecting an ideal or near-optimal therapy challenging, especially among therapy-experienced patients. Over the last decade, computer-based medication selection that measures viral resistance to pharmaceuticals has become a norm for HIV patients. We explore the qualities of available systems and the field's viewpoints.

## INTRODUCTION

HIV is one of the most rapidly changing diseases known, and there is currently no HIV vaccine (1). Because the patient cannot be treated for the virus once infected, therapy aims to inhibit viral replication, alleviate symptoms, and extend life (2, 3). For this goal, more than two dozen distinct antiretroviral medications have been produced in record time for all other illnesses today (4, 5). Drugs inhibit a multitude of phases in the viral replication cycle (6-8). Although a particular medicine therapy can be beneficial for a long time, even years, the virus ultimately evolves into a resistant variety, resulting in therapeutic failure (9). When this occurs, a new treatment combination that effectively addresses the resistance profile displayed by the viral population currently in the patient must be chosen (10). This is a challenging undertaking, but appropriate tools can assist in selecting effective therapeutic alternatives for these individuals (11). This paper summarizes the history and current state of bioinformatics-based resistance analysis and future prospects (12).

### *HIV medication resistance assessment history*

There are two methods for HIV and other viral resistance analyses. Viruses are tested in vitro for sensitivity to various medicines in phenotypic resistance tests (13). This laboratory approach is highly informative in the context of research (14). However, it is unsuitable for clinical routine testing for numerous reasons: the assay is challenging, requiring only a few highly specialized laboratories to do it, it is costly, and it takes a long time (more than a week) (15). Another option is genotypic resistance evaluation, which involves sequencing the relevant sections of the virus genome while analyzing the sequence concerning the virus's resistance phenotype (16). In industrialized nations, genotypic resistance screening is frequently used as a companion diagnosis in HIV therapy (17). The first attempt to analyse genotypic resistance information related to HIV in history was made utilising tables by expert committees that convened regularly (18). They made judgements based on evidence from the literature, laboratory data, and clinical (19). Regular updates to the resultant mutation lists were and continue to be released (20).

The mutation list has improved the efficacy of currently used antiretroviral treatments, but it has two shortcomings: The first is the table's minimal information content (21). A table, in particular, cannot convey relationships between alterations; instead, each mutation functions independently in giving the virus's resistance to the treatment, and neither the epistemic process nor desensitization is considered (22). The emergence of computerized rules-based systems has solved this constraint (23). In effect, they are sets of rules that can assume more sophisticated forms than the rules implied in the mutation tables (24). Consider the rule that says a virus is resistant to medication D if it possesses mutation M1 but not M2 (25). This

describes the virus's desensitization to medication D due to mutation M2 (26). The computer evaluates the relevant region of a viral genome versus all rules in the set in a rules-based system, also known as a resistance algorithm (27). There are numerous widely used systems, including those provided by the Stanford HIV Archive, Rega Institute, and ANRS (28). These techniques form the foundation of computer-based genotypic resistance data interpretation as additional testing for antiretroviral HIV medication selection (29).

*HIV-1 Life Cycle Factors as Anti-HIV-1 Agent Targets*

The HIV-1 life cycle is comprised of multiple phases, beginning with the adherence of an HIV-1 particle to the host cell membrane, where linkages between the HIV-1 envelope (gp120) and the cell surface CD4 receptor proceed by binding to the chemokine receptors CXCR4 or CCR5 (30). These contacts activate the HIV-1 fusion protein (gp41), producing cell-viral membrane fusion (31). The virion's contents are then released into the cytoplasm, where viral RNA is converted to double-stranded DNA by RNA-dependent DNA polymerase or HIV-1 reverse transcriptase (HIV-1-RT) (32).

Following that, viral DNA is incorporated into the host chromosome (33). Translation and transcription Using the cell's machinery, Gag and Gag-Pol polyproteins are converted into viral proteins and transported to the cell membrane, where virions are assembled, budded, and matured before being released as functional HIV-1 particles (34). In general, anti-HIV-1 medications should target viral or cellular proteins in the HIV-1 life cycle (35). Furthermore, interactions between such small compounds and target proteins should ideally result in HIV-1-specific inhibitory effects with minimal toxicity (36).

*Molecular docking of HIV protease Inhibitors*

Six authorized anti-HIV medications were chosen for testing (37). Although 3CLpro-2 and 3CLpro-1 have greater binding energies than all HIV protease inhibitor combinations used as positive controls, 3CLpro-2 has lower binding energy for all investigated inhibitors than its sibling 3CLpro-1 (38). This indicates that 3Clpro-2 has more remarkable binding affinities for inhibitors than 3CLpro-1 (39). Indinavir and darunavir have been shown to have a greater binding capacity to 3CLpro-2 than the other HIV protease inhibitors, and their interaction energy values are comparable to those of HIV inhibitors of protease (40).

When examined, the binding energy of the 3CLpro-2-darunavir complex (-10.24 kJ mol 1) is lower than that of its 3CLpro-2 indinavir equivalent (-10.02 kJ mol 1), showing that darunavir likely has a better affinity for 3CLpro-2 than indinavir (41). Because 3Clpro is required for coronavirus replication, the inhibitory action of these substances on 3Clpro-2 suggests they might be used as anti-COVID-19 therapeutic medicines (42).

*New insights into the clinically validated antiretroviral targets*

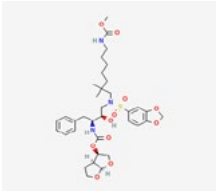
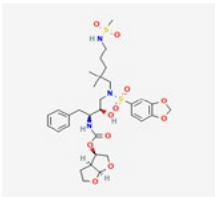
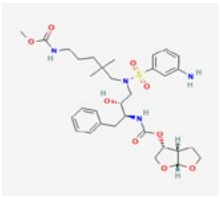
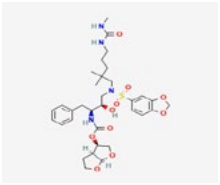
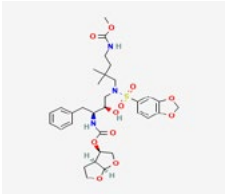
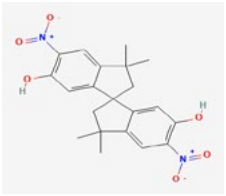
For the clinically validated HIV targets (RT, IN, PR, and CCR5), there is still significant scope for further development of novel inhibitors with distinct mechanisms of action, such as RNase H inhibitors, Nucleotide-competing RT inhibitors (NcRTIs), noncatalytic site (allosteric) IN inhibitors, and PR dimerization inhibitors From the HIV therapy point of view (43), an allosteric inhibitor could restore the potency of an active site inhibitor against multidrug restore the potency of an active, so combined therapy with an active site inhibitor and an allosteric inhibitor may be available as a new anti-HIV strategy to overcome drug resistance (44).

Recently, a high-resolution crystal structure of human CCR5 bound to the approved drug revealed a ligand-binding pocket that is distinct from the putative major binding sites for chemokines and HIV gp120, affording unprecedented insight into the mechanism of allosteric modulation of chemokine signalling and viral entry (45). This structure may suggest potential news that could further inhibit the bioactivity of CCR5 (46). In addition, a subpocket on the N-trimer of HIV-1 gp41 was identified, with implications for developing anti-HIV entry inhibitors (47). Besides targeting an unconventional binding site, another rational design strategy to combat drug resistance has been to maximize highly conserved site interactions and significantly enhance extensive H-bond interactions with main-chain atoms strategy has been extensively employed to seek a variety (48).

*HIV Treatment*

Current anti-HIV medicines inhibit critical phases in the HIV life cycle; nevertheless, HIV can mutate, leaving these medications ineffective (49). HIV therapy is typically administered with two or three groups of ARVs, a process known as cART (50). ARVs are classified into five types: non-nucleoside reverse transcriptase drugs, protease inhibitors, entry/fusion inhibitors, integrase inhibitors, and nucleoside/nucleotide reverse transcriptase agents (51). The three medications of choice are an integrase-strand transfer blocker and two nucleoside reverse transcriptase inhibitors (52). ARVs are administered regularly, making adherence challenging (53). Any disruption in this everyday routine may result in the virus resurfacing (54). ARVs are administered orally; hence absorption is the primary method (55). Long-acting injectables (LAIs) such as Cabenuva, on the other hand, are injected intramuscularly rather than orally, giving LAIs an advantage over orally administered

**Table 1.** Substances retrieved from PubChem have been shown to inhibit HIV-1 protease in vitro.

| Compound | Compound ID | Molecular Formula | Structure | HIV Protease activity |
|---|---|---|---|---|
| **arylsulfonamide 15** | CID480447 | $C_{35}H_{49}N_3O_{11}S$ |  | Active |
| **arylsulfonamide 16c** | CID514961 | $C_{32}H_{45}N_3O_{11}S_2$ |  | Active |
| **arylsulfonamide 11b** | CID480469 | $C_{32}H_{46}N_4O_9S$ |  | Active |
| **arylsulfonamide 16b** | CID480440 | $C_{33}H_{46}N_4O_{10}S$ |  | Active |
| **arylsulfonamide 13** | CID480441 | $C_{32}H_{43}N_3O_{11}S$ |  | Active |
| **CHEMBL60433** | CID478338 | $C_{21}H_{22}N_2O_6$ |  | Inactive |

medicines (56). The ARVs' biodistribution was also studied (57). New research, the first to evaluate ARV concentration from human brain tissues, found a greater concentration than any previously reported concentration (58). Furthermore, various ARVs might be more concentrated in different tissues, implying that particular phases in the HIV life cycle are not inhibited in specific reservoirs (59). As a result, ARV treatment considers medication-to-drug interactions, which may increase drug toxicity (60). Furthermore, some HIV patients use marijuana medically or recreationally, which can block the cytochrome P450 enzymes (61). This can eventually lead to increased ARV concentration in the circulation, which increases adverse effects and excretion rates (62).

*Therapy prediction engines*

A virtual phenotype is an estimate of the result of a laboratory experiment that serves as the foundation for selecting a suitable therapy in a second manual phase (63). The goal of therapy prediction engines is to automate the second stage (64). They rate various therapeutic alternatives in terms of their chance of success for a particular patient (65). Therapy prediction engines tackle a considerably more complex problem than virtual phenotypes since they try to predict clinical outcomes rather than merely a laboratory readout (66). The caretaker then chooses an appropriate therapy from the top-ranking treatments supplied by the prediction engine (67). In doing so, she will consider patient criteria the prediction engine does not evaluate, such as adverse reactions and ease of use (68).

The early treatment prediction engines constructed resistance ratings from virtual phenotypes relatively simply (69). Examples include the genotypic susceptibility score (GSS), a normalized sum of the virus's resistance ratings against several treatment types (70). More advanced systems use cutting-edge statistical learning methods to provide a prediction which involves both the estimated viral resistance and more details, such as drug interactions and an estimate of the virus's expected evolutionary development to escape therapy in the future (71). Therapy forecasting systems can use the predictions provided by virtual phenotypes to predict therapy efficacy (72). Still, they can also use clinical correlates, information on patient history - such as previous use of drugs or combinations of drugs and previously observed resistance mutations - and even information on patient genotypes - such as HLA alleles (73). Several therapeutic prediction systems (THEO from the geno2pheno suite, the EuResist prognosis engine, and the RDI TREPS system) have been published and are available on the Internet (74). Furthermore, positions are under pressure from HLA presentation and certain antiviral medications (75).

## CONCLUSIONS

Computer-assisted HIV treatment is at the forefront of personalized medicine. It is distinguished by complicated genomic biomarkers - essential portions of the viral genome - and a wide range of therapeutic alternatives. The therapy decision problem is dictated by viral resistance and is difficult, if possible, to solve manually. There are two versions of treatment selection systems. The first generation of virtual phenotypes predicts the virus's resistance to any given medicine in the arsenal. Virtual phenotypes are now used in clinical settings. The second generation of therapy prediction engines combines information about a patient, such as resistance estimations, patient history, and clinical correlations. Therapeutic prediction engines, which forecast the likelihood of therapeutic success, are the subject of much research. They are currently employed in research settings but have yet to reach clinical use.

The technique that has proven effective for HIV therapy can potentially be used to treat other infectious illnesses. A fast-increasing arsenal of antiviral medications is developing for HCV infection, leading to hepatitis C and hepatocellular cancer, and combination treatment therapy will become commonplace in the coming years. The geno2pheno

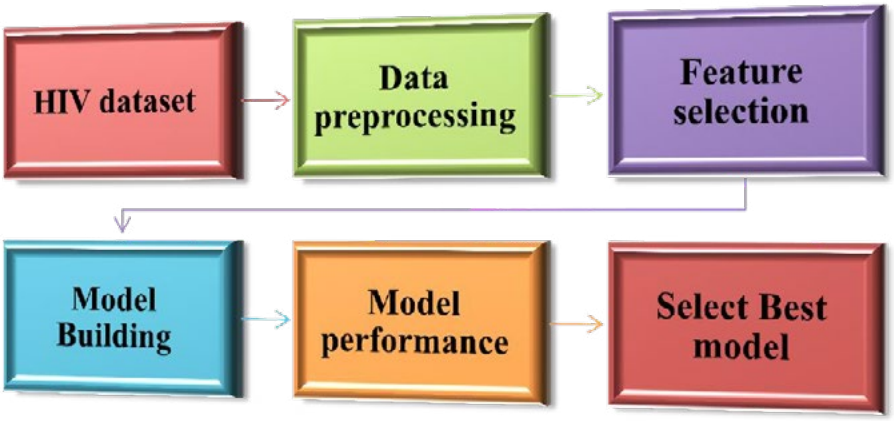



**Fig 1.** Flowchart of machine learning for HIV-failure prediction based on personalized medicine.

service already provides a virtual phenotype of HCV treatment resistance based on guidelines. With more phenotypic resistance data, we are prepared to give a mathematical model of drug resistance on that server. However, it is unknown if such a change is as essential for HCV as it is for HIV. There is optimism that individuals can quickly be cleansed of the virus using extremely efficient combination therapy treatments against HCV. This might reduce the requirement for computer-assisted therapy selection, as shown in TB when essential tabular criteria for medication administration suffice. Another situation in which this technique may be helpful is the HBV infection leading to hepatitis B, although its importance is unknown.

Using this kind of technology to combat tumors in the future has enormous promise. Cancer is similar to an HIV infection in that a parasite genome gains over the management of the cell, develops quickly, and escapes to resistant versions when challenged with medication therapy. The parasitic genome in cancer is that of the tumor cell. Compared to HIV, the genome and the pathways for resistance development are far more complicated and varied. Both situations share the problem caused by the variability of the parasite genome population. In this regard, the links between HIV and cancer are further examined.

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*Conflict of Interest*

The authors declare no conflict of interest.

*Data Availability Statement*

The data generated or analyzed during this study are included in this article.

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