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# The Effectiveness of Protease Inhibitors in the Campaign against HIV/AIDS: A Closer Look at the Critical Factors of ART Compliance and Survival

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## Abstract

One of the most effective ways to decrease the replication of HIV and viral load in HIV-infected patients is to limit the virus' protease enzyme system. Medications that inhibit the HIV protease enzyme system have been shown to decrease mortality. Protease inhibitors attack a vital point in the viral replication cycle. Medical research has shown that this class of drugs increases survival and decreases morbidity in the HIV-infected population. However, protease inhibitors have specific side effects, adversely affecting patient compliance, comorbidities, and mortality. The first-generation HIV drugs (and treatment regimes) have been replaced by newer drugs and drug combinations, presenting fewer side effects and higher compliance rates. This paper reviews the following:topics: the history and development of protease inhibitors, resistance and mutations in HIV-drug therapy, the impact of ART on adverse effects, treatment compliance, drug affordability, mortality, supporting research for protease inhibitors, metrics of ART effectiveness, and HIV-patient survival. The current use of protease inhibitors—although not a cure for HIV/AIDS—is valuable in controlling HIV and decreasing associated mortality and morbidity.

***Keywords:*** *AIDS; Immunodeficiency; HIV; Protease Inhibitor; Survival Rate*

## Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; ART: Antiretroviral Treatment; ARV: Antiretroviral; ATLAS: Antiretroviral Therapy as Long-Acting Suppression; CDC: The Centers for Disease Control and Prevention; FDA: United States Food and Drug Administration; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; MACS: Multicenter AIDS Cohort Study; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NAP: National AIDS Program; NHSO: National Health Security Office; PI: Protease Inhibitor; QoL: Quality of Life; RT: Reverse Transcriptase; SALT: Simplification to Atazanavir/Ritonavir Plus Lamivudine Trial; USDHHS: U.S. Department of Health and Human Services; UNAIDS: United Nations AIDS Organization; WHO: World Health Organization

## Preface

Research has shown an increase in survival for persons living with HIV infection. This increased survival is partly due to better treatment compliance, improvements in medical care, and drug development. Although mortality in the HIV-infected population has decreased over the years, it remains higher than the general non-HIV population. This research evaluated antiretroviral medication regimes containing protease inhibitors to determine if survival rates improved using such.

Data was sourced from eligible studies (Africa, China, France, Malaysia, Rwanda, United Kingdom, and United States). Eleven studies met eligibility criteria (total n = 459,703). The random model was used for effect size. The risk ratio (RR) for death was 0.116 (95% CI:

0.115 - 0.117, p = 0.04). Out of 459,703 people, 39,912 (8.7%) died, and 419,791 (91.3%) survived while on antiretroviral therapy. The Kaplan-Meier survival probability range was 0.61 to 0.95. Heterogeneity for the analysis was determined by Tau-squared and I-squared (0.727 and 99.95, respectively). The Odd ratio was 0.008 (95% CI: 0.003 to 0.020).

The foundational research indicated an improved survival rate with antiretroviral therapy that included a protease inhibitor for people living with HIV. Protease inhibitors seem to have fewer adverse effects, resulting in enhanced patient compliance, which may contribute to the survival rate of HIV-infected individuals.

## Introduction

As the life expectancy and survival rate of HIV-infected patients continues to increase, it becomes pertinent to reassess treatment modalities to determine whether benefits versus risks are still valid for specific drug regimes. Other medications might provide similar positive outcomes with less adverse effects.

Although randomized clinical trials provide strong evidence for treating patients with CD4+ < 200 T-cells/$mm^3$, the optimal time to initiate antiretroviral therapy among asymptomatic patients with $CD4^+$ T-cell counts > 200 cells/$mm^3$ is unknown [1]. All medications offer benefits and side effects [2]. Research has shown that it is better to find minimally intrusive and maximally effective pharmaceuticals, resulting in the least amount of adverse effects in the patient [3]. Experience has shown that combining various regimes that produce high levels of untoward effects and morbidity results in noncompliance by patients [4]. Thus, determining survival rates with medications having minimum adverse effects might enhance treatment compliance among HIV-infected patients.

### The history and development of HIV medications

At the beginning of the HIV epidemic, there were no medicinal compounds available to treat or stop its advance. Early treatment modalities proved inefficient in preventing the progression of the disease. In the absence of pharmaceuticals, authorities focused on preventive care [5]. It was not until 1987, when the first medication was brought to the market. That new medication was zidovudine (AZT). Zidovudine attacks HIV at the reverse transcription step in the HIV life cycle [6]. Thus, it prevents virus replication by inhibiting the enzyme, reverse transcriptase.

It was soon discovered that this medication only slowed the disease's progression, and did not eradicate it. Infected people could still transmit the virus to others. Also, death was prolonged, not prevented. More research was needed. Subsequently, additional medications came to the market in the same drug class. These medications also attacked the HIV life cycle at the same step, reverse transcription [7].

Consequently, when resistance developed, it was typically for the entire class of these medicines (nucleoside reverse transcriptase inhibitors). While the nucleoside reverse transcriptase inhibitors were the first HIV-specific medications, it was not until the approval of protease inhibitors (PIs) that the treatment and outcome changed. Unlike the nucleoside reverse transcriptase inhibitors, the PIs targeted a late stage in HIV replication. They inhibited the HIV protease enzyme from cleaving cells required for HIV replication [8].

With the addition of protease inhibitors to nucleoside reverse transcriptase inhibitors (NRTIs), the combined medicines could intervene in the HIV life cycle at various stages. Soon thereafter, a third antiretroviral class of medicines, known as non-nucleoside reverse transcriptase inhibitors (NNRTIs), was introduced, allowing for "triple-therapy" against HIV [9]. HIV-positive patients could now be treated by various combinations of these medications, assailing the HIV life cycle at different points [10]. The drug combination worked synergistically, inhibiting viral replication [11]. However, many patients could not remain compliant with the drug regime for various reasons, physical, financial, and dosing.

The new drug regime required taking many pills daily, resulting in side effects, toxicity, and complicated drug interactions [12]. Nonetheless, after dosage and combination adjustments (to maximize potency and reduce side effects), the regime became a highly active antiretroviral therapy (HAART) treatment [13]. Although HAART is not a cure for HIV, it changed HIV from a mortality health statistic to a manageable chronic disease [14]. Currently, HAART is referred to as antiretroviral therapy (ART). The medical community adopted the new nomenclature as the drug regime evolved [12].

**ART: impact on mortality**

Before the advent of ART treatment, AIDS-related deaths had surpassed cancer, homicide/suicide, and unintentional injuries as the leading cause of death in the 25–44 age bracket for men [15]. Approximately 56,300 new HIV infections occurred in the United States in 2006. However, the HIV mortality rate has decreased. This decrease can be attributed to ART treatment [16,17]. Some of the deterrents to adequate medication treatment involve compliance, side effects, and economic affordability [18].

**ART: compliance, affordability, and adverse effects**

People with HIV rely on a daily regime of medications to extend their life and decrease morbidity. Thus, medication compliance is the best method for controlling the symptoms of HIV [19]. Noncompliant patients allow the virus time to replicate and become resistant to HIV medications. Resistance to HIV medications results in a rapid decline in an HIV-infected patient's condition [20]. Thus, medication adherence is a crucial feature of disease control.

There are several reasons for noncompliance. The earlier HIV medications produced significant side effects [21,22]. Many patients became too ill from the side effects to comply with the medications. Some medications caused secondary mortality [23]. For example, many persons on HIV medication developed liver failure and died from its complications [24–26]. The actual cause of death in many patients was not always an opportunistic infection but organ failure due to a medicine's adverse effects [27]. HIV medications can cause gastrointestinal and hepatic cell damage, resulting in lipid imbalance and sexual dysfunction [28–30]. When the side effects of the HIV medicines are pronounced, a corresponding decrease in activities of daily living results.

A study conducted with HAART found that more patients discontinued antiretroviral therapy due to adverse events than any other cause [31–33]. Side effects like sexual dysfunction, liver complications, and gastrointestinal upset were some of the most frequent complaints by patients [34–37]. Because of these untoward side effects, many individuals discontinue the medication. Diminished quality of life (QoL) due to adverse effects became the main reason for HIV patients discontinuing their medication.

In the early years of HIV-medication regimes, some individuals took as many as 10–11 pills 3–4 times a day. This pill-burden fostered noncompliance [38,39]. Pharmaceutical companies addressed this problem by combining various medicinal ingredients into one pill. This breakthrough in reducing the number of pills taken daily helped the HIV community enormously. The massive pill burden was now reduced to 1 or 2 pills daily [5,40,41].

The financial burden (cost of the medication) was another cause of noncompliance [18]. Many people in the HIV community did not have adequate or any health insurance [42]. This under-coverage or lack-of-coverage hampered adherence. During the treatment of a chronic disease, like HIV, physician appointments, medication regimes, and health-related behaviors must remain consistent. Individuals who are economically challenged tend to visit the physician less than those with adequate funds, and are less compliant with medications [43,44].

Frequently, physicians prescribed medications and multiple follow-up appointments without considering the economic impact to the patient. Medical treatment, compliance, and follow-up by HIV patients were significantly impacted by social and economic factors. Thus,

medical providers had to evaluate social and economic factors regarding patient compliance. Considering all factors, yields enhanced adherence to HIV treatment protocol [45].

**The history and development of protease inhibitors**

According to Sapkale *et al*. (2013): HIV protease inhibitors were developed between 1989 and 1994 by researchers working for the pharmaceutical companies of Hoffmann-La Roche, Inc. and Abbott Laboratories with Merck & Co., Inc. Hoffmann-La Roche, Inc. conceived the first HIV protease inhibitor trade name, Invirase (saquinavir-FDA approved in 1995). Abbott Laboratories later developed protease inhibitors Norvir (ritonavir: FDA approved in 1996) and Kaletra (lopinavir/ritonavir: FDA approved in 2000). Saquinavir and ritonavir were approved in 1995–1996 for medicinal use. Merck & Co.'s researchers conceived the HIV protease inhibitor trade name, Crixivan (indinavir: FDA approved in 1996), while Agouron Pharmaceuticals developed Viracept (nelfinavir: FDA approved in 1997). Agenerase (amprenavir: FDA approved in 1999) was marketed by Glaxo Wellcome, Inc. (licensed from Vertex Pharmaceuticals) [46].

These early phase protease inhibitors (year 2000 and earlier) changed the strategy in the fight against HIV. Phase 2 protease inhibitors were designed to reduce the pill burden on patients [47]. The first once-daily dosing inhibitor originated in 2003, by the name of atazanavir. The second-generation protease inhibitors offered advantages of reduced dosing and fewer side effects [48,49]. Another advantage of the second-generation protease inhibitors was reduced mutations to the original chemical compound [50–52].

PIs are synthetic drugs that inhibit the action of HIV-1 protease, an enzyme that cleaves two precursor proteins into smaller fragments. These fragments are needed for viral contagion, growth, and duplication [53]. PIs bind to the protease enzyme's active site, preventing maturation in new virions [54]. The fragments become non-infectious. Currently, fourteen protease inhibitors are available in the medical marketplace.

**Research in support of protease inhibitors**

PIs are effective at delaying HIV progression and replication. They have been the main contributor to decreasing morbidity and mortality for over 20 years [55]. In the clinical setting, specific PIs are combined with the protease inhibitor ritonavir to boost their conjoined medicinal potency [6]. Ritonavir has strong cytochrome $P_{450}$ CYP3A and 2C8 properties. Ritonavir is also an inducer of the 1A2, 2B6, and 2C9 isoenzymes [56]. Thus, it can enhance plasma concentrations of other protease inhibitors. The advantage is higher trough levels with an extended drug half-life, which improves effectiveness and decreases the risk of resistance [57].

Cobicistat is also an inhibitor of $P_{450}$ CYP2D6 used with protease inhibitors. The purpose is the same as ritonavir. It allows for lower doses and reduces dosing frequency. Most PIs combine ritonavir or cobicistat into one capsule to reduce the pill burden [58]. Another advantage of this process is the reduced cost for patients. The cost associated with a high pill burden is often prohibitive to patients and, thus, adversely affects patient compliance [59,60]. This novel mixture of medicines enhances outcomes in HIV-patient treatment.

The benefits of PIs in the campaign against HIV is well documented in the literature [61] as excerpted and summarized from the following studies and trials.

In 2015, the Antiretroviral Therapy as Long-Acting Suppression (ATLAS) trial determined that an antiretroviral regimen consisting of lopinavir/ritonavir or atazanavir plus a single NRTI may be sufficient to maintain HIV suppression in most patients. The study included 266 patients; 78% were men, and the median age was 44 years. The average CD4 count was 600 cells/$mm^3$. At the start of the trial, most patients were taking atazanavir/ritonavir with two NRTIs. Tenofovir and emtricitabine were the NRTIs taken by most participants (79%). Patients had suppressed viral loads (< 50 copies/mL) for at least three months with no virologic treatment failure. Participants in this open-label study were randomized to either stay on the same regimen or switch to atazanavir/ritonavir plus lamivudine [62].

At 48 weeks, 90% of the patients who switched to dual dual-therapy and 80% who stayed on triple-therapy maintained viral suppression in an intention-to-treat analysis. Two persons (1.6%) in the dual-therapy arm and six persons (4.7%) in the triple-therapy section experienced virologic failure [62].

The Global AntiRetroviral Design Encompassing Lopinavir/r and Lamivudine vs. LPV/r-based standard therapy trial (GARDEL) included 306 untreated persons with HIV from Argentina, Chile, Mexico, Peru, Spain, and the United States. Patients were followed for 96 weeks. Eighty-five percent of the participants were men, with a median age of 35 years. The median baseline CD4 cell count was 325 cells/$mm^3$ (43%), with a viral load of HIV RNA > 100,000 copies/mL. At the start of the trial, no patient had known NRTI or PI resistance mutations [63].

Participants in this open-label study were randomly assigned to receive 400/100 mg lopinavir/ritonavir plus 150 mg lamivudine twice-daily, or lopinavir/ritonavir plus two NRTIs either abacavir/lamivudine (9%), tenofovir/emtricitabine (37%), or zidovudine/lamivudine (54%). The differences between the regimens were due to host country variation in guidelines for NRTIs. The results at 48 weeks showed 88.3 % of the participants taking the dual-regimen, and 83.7 % of the participants taking the triple-regimen had an undetectable viral load (< 50 copies/mL) in an intention-to-treat analysis (difference 4.6%, 95% CI -2.2 to 11.8; p = 0.171). Thus, the simplified regimen was non-inferior to standard therapy. Also, at 48 weeks, 87.2 % of the participants on dual-therapy and 77.9 % of those on triple-therapy maintained viral suppression (87.2% vs. 77.9%, respectively; difference 9.3%, 95% CI -2.8 to 21.5; p = 0.145 [63].

High baseline viral-load individuals had similar response rates: 91% vs. 81%, respectively. The as-treated analysis rates were 93% and 97%, with mean CD4 cell gains similar in the two treatment arms: 300 and 310 cells/$mm^3$, respectively [63,64].

The OLE/RIS-EST13 Study Group (OLE) trial compared lopinavir/ritonavir and lamivudine to lopinavir/ritonavir plus two NRTIs. The study was conducted between October 2011 and April 2013, with 250 participants on triple-treatment, 127 (51%) on standard therapy, while 123 (49%) were switched to dual-treatment. In the intention-to-treat population, 110 (86.6%) of 127 patients in the triple-treatment group responded to treatment versus 108 (87.8%) of 123 in the dual-treatment group (difference −1.2%; 95% CI −9·6 to 7.3; p = 0.92). These results met the criteria for non-inferiority treatment. Serious adverse events occurred in 8 patients (7%) in the triple-treatment group and 5 patients (4%) in the dual-treatment group (p = 0.515). Four patients (3%) in the triple-treatment group and one patient (1%) in the dual-treatment group (p = 0·223) discontinued treatment due to adverse events [65].

The Simplification to Atazanavir/Ritonavir plus Lamivudine Trial (SALT) randomly assigned 286 patients (143 in each of two groups). The inclusion criteria included: age 18 or older, HIV RNA < 50 copies/ml for more than ≥ 6 months, no recent changes in ART in the previous 4 months, no previous virologic failure, and no known resistance to the study's drugs. Measurements were taken at 48 weeks and 96 weeks [66].

One group was treated with dual-therapy, atazanavir 300 mg/ritonavir 100mg plus lamivudine 300mg (ATV/r+3TC). The other group used triple-therapy, atazanavir 300 mg/ritonavir 100 mg plus two NRTIs (ATV/r+2NUCs). At week-96 of the study, 74.4% had HIV-1-RNA < 50 copies/mL in the ATV/r+3TC group versus 73.9% in the ATV/r+2NUCs group (95% CI for the difference, -9.9%-11.0%) [66].

In contrast, at 48 weeks, 105 of 135 patients (78%) in the triple-treatment group (difference 6%: 95% CI -5 to 16%) had a response showing non-inferiority. Severe adverse effects were reported in 14 patients (5%) in the dual-treatment group and eight patients (6%) in the triple-treatment group. At week-96, the grade 3 to 4 adverse events were 70.7% versus 70.2% -0.3 (95% CI, -0.5 to -0.1) for ATV/r+3TC, versus -0.2 (95% CI, -0.4 to -0.1) for ATV/r+2NUCs] [66].

At week-48, the grade 3 to 4 adverse events were similar between groups: the dual-treatment group was 77 of 140 (55%), while the triple-treatment group was 78 of 141 (55%). Treatment discontinuations were less frequent in the dual-treatment group compared to

the triple-treatment group. There were three discontinuations (2%) for the dual-treatment group and ten discontinuations (7%) for the triple-treatment group (p = 0.047) [66].

Thus, dual-treatment was effective, safe, and non-inferior to triple-treatment in patients with HIV-1 infection. The researchers also concluded that dual-treatment was effective in individuals who were virologically suppressed, but needed to switch antiretroviral therapy regimens due to toxic adverse reactions and intolerance. Dual-treatment could decrease some of the long-term toxic effects accompanying NRTIs, while preserving future treatment options at a reduced cost [61].

The DUAL-GESIDA-8014-RIS-EST45 Trial recruited individuals with an undetectable viral load on a regimen of darunavir/ritonavir plus either tenofovir/emtricitabine or abacavir/lamivudine. Participants could continue to take their existing regimen or switch to a basic regimen of darunavir/ritonavir plus lamivudine. All regimens were dosed once daily [67].

This combination was chosen because ritonavir was the only recommended protease inhibitor used as a pharmacokinetic booster for other protease inhibitors in European and United States guidelines. The study was conducted in Spain. The DUAL study randomized 249 people with an undetectable viral load into one of two groups. The first group was placed on darunavir/ritonavir plus either tenofovir/emtricitabine or abacavir/lamivudine. The second group continued taking their existing regimen or were switched to a regimen of darunavir/ritonavir plus lamivudine [67].

The researchers enlisted individuals with no evidence of resistance to darunavir or lamivudine. The participants also had to have a suppressed viral load for at least six months on a regimen of darunavir/ritonavir plus either abacavir/lamivudine or tenofovir/emtricitabine. Three-quarters of participants (75%) were taking tenofovir/emtricitabine, and 25% were taking abacavir/lamivudine after randomization. The study's demographics were as follows: 83% male, 85% Caucasian, 51% men who have sex with men, 27% heterosexual, and 15% who injected drugs. The 15% ethnic make-up of the other individuals in the study was not noted. Participants were on treatment with a fully suppressed viral load for an average of 100 weeks. The average CD4 cell count was 589 cells/$mm^3$ at the time of randomization [67].

After 48 weeks, there was no significant difference in the proportion of participants in each study group. Eighty-nine percent of those on the simplified regimen had viral load < 50 copies/ml at week-48, compared to 93% in the triple-drug regimen group by intent-to-treat. Hence, the dual-regimen study group missed an equal failure analysis. The researchers clarified that more participants in the two-drug arm had missing information (viral load data) at the week-48 clinic visit (5% vs. 2%) than the other group. The reason for the missing data was not reported [67].

Single viral load increases were somewhat more frequent in those receiving a triple-drug regimen (13.2% vs. 8.9%); however, this difference was not statistically significant. Of the individuals receiving the two-drug regimen, 4.5% had two viral load event increases compared to 2.6% in the triple-drug group. Researchers were able to do resistance testing in five individuals who had virologic rebound above 400 copies/ml. Genotype failure was noted in two of the five cases. Resistance to darunavir was detectable in one participant on the triple-drug regimen [67].

There was no significant difference in serious adverse events between the dual-drug and triple-drug study groups (4.8 vs. 4.9%). Drug discontinuations due to adverse events were similar (0.8 vs. 1.6%). No significant improvement in kidney function or total cholesterol/HDL cholesterol ratio was observed in those who switched to the simplified regimen [67].

Researcher José Perez-Molina (2017) conducted a meta-analysis on dual-HIV treatments versus other regimens by combining data from four fundamental studies (SALT, OLE, DUAL, and ATLAS). Recall that the SALT study compared atazanavir/ritonavir and lamivu-

dine to atazanavir/ritonavir plus two NRTIs. The OLE trial compared lopinavir/ritonavir and lamivudine to lopinavir/ritonavir plus two NRTIs. The DUAL study compared darunavir/ritonavir and lamivudine to darunavir/ritonavir plus tenofovir/emtricitabine or abacavir/lamivudine. The ATLAS trial compared atazanavir/ritonavir and lamivudine to atazanavir/ritonavir plus two NRTIs [68].

The researcher's goal in conducting a meta-analysis was to determine if using a two-drug treatment was inferior to using a three-drug treatment by effect size. A study goal was to consider new FDA guidelines defining when an adjustment to a regimen should be considered virologically non-inferior. (The standard was a 4% margin of non-inferiority.) An additional goal was to determine if boosted protease inhibitors were inferior to others when used as part of a two-drug regimen [68].

The combined four studies included 1051 individuals. The study performed an analysis at week-48. The meta-analysis results concluded that there was no significant difference in individuals according to viral load (below 50 copies/ml- noted as undetectable). Persons taking dual-therapy (84.7%) had a viral load < 50 copies/ml compared to 83.2% of the people taking a three-drug combination. The difference supported dual-therapy 1.47% (95% confidence interval -2.9% to 5.8%) [68].

Similarly, there was no difference in people who had a detectable viral load (> 50 copies/ml) at week-48. This measure was used to differentiate between people who had experienced a viral rebound and those who had discontinued treatment for other reasons. The dual-therapy group had a 4% detectable viral load while the three-drug group had a 3.04% detectable viral load: a difference of 0.9% (95% CI -1.3% to 3.2%) [68].

This meta-analysis displayed smaller confidence limits than the individual clinical trials. The analysis also found no difference in outcome for either measure when the three boosted protease inhibitors used in these studies were compared. The researchers also concluded that gender and coinfection with hepatitis C during the study did not influence the results [68]. Thus, this meta-analysis provided additional support for the use of PIs in a simplified regimen to enhance compliance, suppress viral load, and reduce morbidity.

**Resistance and mutations with drug therapy**

Resistance to medication occurs through various mechanisms. Viral mutation at the molecular level and patient adherence play roles in resistance. HIV is part of the retrovirus family. Retroviruses have a high mutation rate due to copy errors during replication from the lack of proofreading to correct those errors [69]. Retroviruses do not proofread 3`→ 5` exonuclease activity of the virion-encoded RNA polymerase [19]. Thus, RNA polymerase makes many errors during replication.

In the viral life cycle, HIV-1 produces viral precursor proteins. The most commonly made proteins are Gag and GagPol [70]. The Gag precursor codes for structural proteins in the virus. The GagPol protein makes three enzymes: reverse transcriptase, protease, and integrase [71]. The protease enzyme cleaves precursor proteins at different sites to facilitate the maturation of viral particles [72]. PIs mimic the substrate of the viral protease. The PI binds to the active site of the enzyme. This binding prevents protease from cleaving Gag and GagPol precursor proteins, resulting in immature non-infectious viruses [73].

As mentioned previously, HIV does not participate in protein proofreading activity, resulting in strains of HIV, sometimes referred to as "wild-type" viruses [74]. These strains are referred to as wild type because these viruses produce normal plus mutated self-copies. It has been estimated that every possible error in the wild-type structure of HIV can occur once every day if viral production is not suppressed with ART [75]. Some of these errors produce defective variants that cannot reproduce. This polymorphistic behavior gives the virus an advantage. Due to mutations, there is no one type of HIV. This polymorphism is how the virus gains resistance against certain antiretrovirals [76].

Resistance occurs when drug levels in the bloodstream are suboptimal to prevent viral reproduction. Low drug levels can have many causes, such as poor adherence caused by missing or incorrectly taking doses [77], medication not absorbed or metabolized correctly due to intestinal malabsorption, or drug-drug and drug-food interactions [78–81]. Depending on the viral mutation, resistance to one drug can cause the virus to become resistant to similar classes of drugs [68] through a process known as cross-resistance [82]. Some individuals are cross-resistant to medications they have never taken.

There has been an increase in resistance to PIs for several years. The initial resistance can differ between the PIs. Most sites of resistance are proximal to the substrate-binding site of the enzyme [83]. Transformation of the substrate-binding site causes interference with the binding of the PI to the viral protease directly or indirectly, causing resistance to PIs [84]. Most PIs differ only slightly in their chemical structure [11]. Thus, viral mutations can lead to concurrent resistance to multiple PIs [85]. As a result, cross-resistance can become a significant issue with protease inhibitor treatment.

Other changes can occur at alternate sites on the virus. Mutations in the protease-cleavage sites of Gag can emerge [86]. These site mutations may change the substrate's structure so that the viral protease is better able to cut its natural substrate [87]. Mutations in Gag outside the cleavage sites have been observed *in vitro* and *in vivo* [88,89]. These mutations seem to compensate for the reduction in replicative capacity caused by mutations; however, it is unclear how this occurs.

HIV can evade protease inhibitor treatment by the initiation of mutations in the protease enzyme. Thus, two methods have been devised to overcome protease inhibitor resistance. The first method is to increase protease inhibitor levels in the blood by giving a low dose of ritonavir [90]. This method will inhibit cytochrome P450-mediated metabolism of PIs, resulting in higher drug plasma levels. The second approach involves PIs with high potency against resistant variants [91]. Applying these new methods requires the virus to produce multiple mutations of the protease enzyme to overcome ART activity [92].

*In vitro* experiments with the new high genetic barrier PI RO033-4649 have shown that HIV can use auxiliary resistance mechanisms. Instead of causing the virus to produce multiple mutations in protease enzymes, it generated mutations in other protease-cleavage sites, resulting in resistance as before [92,93]. Moreover, *in vitro* experiments with another new high genetic barrier PI TMC114, resulted in a resistant virus in the absence of drug-resistance mutations [91].

How resistance mechanisms play a role *in vivo* is unknown. Clinical trials with lopinavir coadministered with a low dose of ritonavir have revealed a virological failure in 20% of ART-naive patients [94]. This failure was not attributed to the development of resistance mutations in the protease enzyme. Although therapy compliance might play a role, additional studies are needed to explore whether alternative resistance mechanisms are involved.

**Resistance testing**

Resistance testing might determine an individual's resistance to a particular drug. There are two types of resistance tests: one given before treatment, the other during active treatment with a viral rebound. These procedures are known as genotypic or phenotypic testing [95]. Most assays detect resistant viruses only if the subpopulation makes up at least 10% to 20% of an individual's total viral population. Currently, the role of low-frequency drug-resistant variants is being explored. It is posited that standard HIV resistance-testing might fail to detect HIV drug resistance in more than one-third of all treatment-naive patients [96]. More sensitive tests are needed to detect smaller populaces of resistant virus.

**HIV-patient survival using protease inhibitors**

Several clinical trials have shown that ART regimens with a PI decrease morbidity and mortality secondary to HIV infection. However, the effect varies across different regions of the globe.

Accordingly, data was explored from different regions. In the past, access to various HIV medications has been disjointed and unequal in distinct countries. Wealthier nations like the UK, USA, and many European countries have better access to HIV medications [97]. Poorer nations tend to have limited or outdated treatment modalities. These economic disparities cause fluctuations in data analysis, depending on where the study was conducted. PIs might appear more effective in wealthier nations than poorer nations based on access to medicines, resistance level, and medical healthcare availability [21,98,99]. However, over the past several years, expanded access to ART has led to substantial reductions in morbidity and mortality across the globe [100].

Measuring life expectancy secondary to ART treatment is a pertinent clinical care outcome. In the United States, the average life expectancy after an HIV diagnosis increased from 10.5 to 22.5 years from 1996 to 2005 [101]. Many extensive cohort studies have validated increased life expectancy due to ART containing protease inhibitors.

The Antiretroviral Therapy Cohort Collaboration was a comprehensive HIV collaboration study, involving North America and European nations. Patients were included if they were aged 16 years or over and were ART-naive when initiating therapy. The researchers evaluated life expectancies for individuals on ART in 1996–99, 2000–02, and 2003–05, respectively. The results were stratified according to sex, CD4 cell count, and history of injecting drug use. The average number of years (remaining to be lived) by persons treated with ART at 20 and 35 years of age was determined. The potential years of life lost from 20 to 64 years of age, and mortality rates were also calculated. The results showed that 18,587, 13,914, and 10,854 eligible patients started ART in 1996–99, 2000–02, and 2003–05, respectively. An estimated 2056 deaths were noted during the study period: a decrease in mortality from 16.3 deaths per 1000 person-years in 1996–99 to 10.0 deaths per 1000 person-years in 2003–05. Probable years of life lost per 1000 person-years also decreased from 366 to 189 years [102]. Consequently, life expectancy at age 20 years increased from 36.1 (SE 0.6) years to 49.4 (0.5) years. Women in the study had higher life expectancies than men. It was not explained why this occurred. In non-HIV-infected persons, women live longer than men [102].

Patients with presumed transmission via injecting drug use had lower life expectancies than those from other transmission groups: 32.6 (1.1) years versus 44.7 (0.3) years in 2003–05. These results might have been influenced by confounding as patient characteristics might have changed throughout treatment. For example, HIV transmission for persons who injected drugs did not necessarily imply continued drug use [102].

Life expectancy was lower in patients with decreased baseline CD4 cell counts (32.4 [1.1] years for CD4 cell counts below 100 cells per μL versus 50.4 [0.4] years for counts of 200 cells per μL or more). In HIV-infected patients treated with ART, life years increased between 1996 and 2005. However, the researchers noted considerable variability between the subgroups of patients. Although years of life gained for the HIV-infected patient were lauded, the average number of years remaining to be lived at age 20 years was about two-thirds of the general population in most ccountries, revealing that living with HIV equates to a shorter life span than non-HIV-infected persons [102].

The Multicenter AIDS Cohort Study (MACS) was a prospective study of HIV-1 infection in homosexual and bisexual men. The study sites were Baltimore, Chicago, Pittsburgh, and Los Angeles. A total of 6,972 men were enrolled. This prospective study started in 1984 and concluded in 2019. The results showed a delayed onset of AIDS and death among HIV-infected men. This research included only bisexual and gay men, the results might not be applicable in different patient populations. Also, the research was carried out in clinics that specialized in HIV treatment. Healthcare practitioner knowledge and above-average patient adherence to medications and treatment regimens might have contributed to a higher than average survival rate [103].

The Danish HIV Cohort Study measured HIV-infected individuals aged 16 years or older at the time of HIV diagnosis. The infected persons were seen in one of eight Danish HIV treatment clinics between December 1994 to 2006. The resarchers enrolled 4720 individuals, the majority being males (3543). They found that persons on ART had a reported decrease in mortality from 1995 to 2006 [104].

The French Hospital Database on HIV study (FHDH-ANRS CO4) comprised 120,542 HIV-infected patients seen at least once between January 1, 1992 and December 31, 2009. There was a median follow-up of 5.6 years. This French study reported a decrease in AIDS-related mortality in persons with HIV on ART. These findings did not include improvised areas of the prospective countries; thus, the results were generalized to people living with HIV in high-income areas [105].

Paradoxically, resource-limited countries have experienced similar gains in HIV life expectancy. In a cohort study by Mills *et al*. (2011), of 22,315 patients starting ART in Uganda, researchers reported increases in life expectancy. An estimated 27.9 years was added when starting ART at age 35 years [106]. Additionally, Ruel *et al*. (2014) explored virologic and immunologic outcomes in HIV-infected children from Uganda and found that ART improved virus control and survival [107]. Likewise, increases were noted in a Rwandan cohort study by Nsanzimana *et al*. (2015), with an addition of 29.9 years after starting ART at 20 years compared to a life expectancy of 51 years for the general population [108].

In Southeast Asia, Thailand has one of the highest prevalence rates of HIV infection [109]. It is estimated that 1% of the population is affected [110]. A lack of healthcare and economic resource limitations can partly be blamed. Therefore, in 2008, the Thai government started to provide universal healthcare coverage for HIV treatment through its National AIDS Program (NAP). The program is administered by the National Health Security Office (NHSO) that keeps citizen data for the country. The NHSO conducted a study from 2008 to 2015 to determine the impact of ART initiation on life expectancy in HIV-positive Thai patients. A total of 201,688 eligible persons were included in the study. The median CD4+ T-cell count was 109 cells/$mm^3$, with a median age of 37 years. The life expectancy after starting ART at age 20 years was 25.4 (95% CI, 25.3, 25.6) years and 20.6 (95% CI, 20.5, 20.7) at age 35 years [111].

South African researchers, Shearer *et al*. (2017), examined retrospectively 1236 HIV-positive patients from 2004 to 2012 who were switched to ART that contained a protease inhibitor. One of the parameters of measurement was survival. The researchers concluded that adult patients on ART had an overall lower mortality rate at one year. Only 2% of the patients died from high rates of virologic suppression [112]. The low levels of mortality observed in the cohort after second-line ART initiation with a protease inhibitor possibly reflects some under-ascertainment of deaths.

A meta-analysis by Teeraananchа *et al*. (2016) comprised eight cohort studies, estimating life expectancy in HIV-infected persons starting ART (aged ≥ 14 years) in high-income countries. A random-effects meta-analysis was used to pool estimated outcomes by country income. Heterogeneity between studies was assessed using the I-squared statistic. It was estimated that high-income countries showed an additional 43.3 years [95% confidence interval (CI) 42.5 – 44.2 years] and 32.2 years (95% CI 30.9 – 33.5 years) at ages 20 and 35 years, respectively. This equated to 28.3 (95% CI 23.3 – 33.3) and 25.6 (95% CI 22.1 – 29.2) additional years in low- to middle-income countries. Thus, in low-to middle-income countries, those who started ART at age 20 years gained an additional 22.9 years (95% CI 18.4 – 27.5 years) for men and 33.0 years (95% CI 30.4 – 35.6 years) for women. In all income regions, life expectancy after starting ART increased over time [110].

Mortality in this meta-analysis was estimated on pooled data, and the estimated life expectancy might have reflected the patients' average experience. Estimates of life expectancy are sensitive to mortality in the oldest age groups [113]. The analysis did not provide this oldest age group data. Most deaths in persons with HIV infection occur in the untreated population. This analysis was limited to persons on ART.

**The metrics of ART effectiveness**

ART efficacy is measured according to CD4 cell count and viral load at one year after initiation. A higher CD4 count and low viral load translate into a stronger immune system. The healthier immune system equals less AIDS-related opportunist infections. AIDS-related and non-AIDS-related mortality decline is the overall outcome. The life expectancy of patients on ART has increased, but remains lower than

in the general population [114].

In the past ten years, various changes to the ART regimen have taken place. New HIV medications have been introduced to the market, such as integrases. HIV medication pharmacokinetics have improved [115]. Older HIV drugs have been paired to increase therapeutic blood levels and minimize resistance [116]. Also, newer drug regimens have improved tolerability with fewer side effects, improving enhancing compliance [117–119]. Heightened compliance can partly explain why patients who started ART during 2008–10 had an estimated life expectancy approaching that of the general population.

While strengthened adherence, drug effectiveness, tolerability, and fewer side-effects can be attributed to the first year's decline in mortality, enhancements in survival during the second and third years are most likely due to viral suppression [120–123]. Another reason for increased survival is improved management of patients with late presentation of HIV infection [124]. General improvements in healthcare for people living with HIV could also have contributed to increased survival. People are now living longer with HIV infection. This has caused a shift in the medical community to treat comorbidities more aggressively [125–127]. Comorbidities like cancer, cardiovascular disease, and hepatitis should be treated aggressively in this patient population [128,129].

In 2010, a National HIV/AIDS Strategy was introduced in the United States with the goal of increasing access to care, improving health outcomes, and addressed health inequities among people living with HIV [130].

**Summary**

The amalgamation of drugs directed at different steps in the HIV life cycle increases therapeutic efficacy, reduces resistance, and lessens drug toxicity. The most utilized antiretroviral medications are ARTs (formally known as HAART) [131]. The ART regimes are a combination of reverse transcriptase inhibitors, protease inhibitors, and or integrase inhibitors. Protease inhibitors are the core components of ART. Two generations of protease inhibitors have been developed since 1995. The first-generation drugs are structural analogs of the Phe-Pro protease cleavage site. They are defined as peptidomimetic inhibitors [41].

There are eight medications in this category: amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir. These drugs are competitive, selective, and reversible inhibitors of HIV-1 and HIV-2 protease enzymes [132]. They block the maturation of the HIV virus and create nonfunctional and noninfectious virions [133]. Atazanavir is an azapeptide protease inhibitor of HIV-1 protease. It differs structurally from other peptidomimetic protease inhibitors by its C-2 symmetric chemical structure [134,135].

The second-generation protease inhibitors are nonpeptidic in structure. This group includes tipranavir and darunavir. The second-generation PIs are more active against HIV-1 strains that are resistant to other protease inhibitors [90,136].

Both generations of protease inhibitors cause side effects. Clinical data has linked protease inhibitors to cardiovascular diseases, diarrhea, dyslipidemia, and hepatic lipotoxicity [95,137,138]. These side effects are major obstacles to compliance. Protease inhibitors that cause significant side effects are less likely to be taken by patients [139,140]. Decreased compliance leads to increased morbidity and mortality [44,141].

The primary goal of ART is the suppression of plasma viremia (< 50 RNA copies/ml) to reduce morbidity and mortality associated with HIV infection. An additional goal of ART is to preserve CD4 + T cell count above 200 cells/ml [142,143]. These levels will delay or stop opportunistic infections, which are the main cause of death in many HIV people. Thus, ART enhances viral suppression and CD4 preservation [144].

Many studies have validated these findings. People living with HIV between 1996 and 2013 on ART realized an increase in survival [78]. During the first year of ART, mortality was similar in patients who started ART between 1996 and 2007. However, it was lower for those who started during 2008–10. Survival improved during the second and third years after initiating ART.

The same decreases in mortality were not seen in IV drug users as in other groups, which can be partly explained by lower compliance, increased resistance, and coinfection with other viruses, like hepatitis. Improvements in survival with ART have provided evidence to healthcare providers, governments, policymakers, and patients that effective treatment can result in normalcy for this chronic disease [145,146]. Once-a-day dosing is now preferred to older antiretroviral drug regimes that cause untoward side effects, adversely affecting compliance.

Increased life expectancy approaching that of the general population is a tool that can be used to motivate noncompliance or at-risk individuals [110]. Since ART is highly effective and has a lower toxicity than earlier HAART regimens of the 1990s, it is thought that mortality will continue to decrease over time [147]. Individuals living with HIV, as well as members of the medical community, can now focus on adherence and non-AIDS comorbidities, such as cardiovascular disease and hypertension [148].

Late diagnosis and follow-up to care must be addressed to decreased mortality. Patients who are first diagnosed at the AIDS stage are less likely to survive than those who are diagnosed at a pre-AIDS level [149]. In 2015, the treatment guidelines changed after the results of the START trial showed benefits from immediate versus deferred treatment. The current standard of treatment for newly diagnosed persons with HIV is to begin ART at the time of diagnosis [150]. However, prompt treatment will only result in improved survival if late diagnosis and access to care are addressed.

## Conclusion

The advanced use of protease inhibitors, as reported herein, is an effective way to lower RNA viral load, decrease morbidity, and increase survival in the HIV-infected population. In some cases, two-drug therapy can be as effective as three-drug therapy. Two-drug therapy decreases some of the long-term toxic effects accompanying nucleoside reverse transcriptase inhibitors while preserving future treatment options at a reduced cost.

## Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

## Supplementary Information

The intention of the authors is to publish three interdependent papers on this topic—this being the second; the first entitled, "The Search for the Most Efficacious Engagement Point in the Campaign Against HIV: A Closer Look at the Life Cycle of the Human Immunodeficiency Virus"; and the third entitled, "Meta-analysis and Rationale Regarding the Effect of Protease Inhibitors on Survival in the HIV-1-Infected Population". The three papers will be made available through E-Cronicon of the United Kingdom by the same team of researchers and authors. This paper is based, in part, on prior research: Pruitt, KD. (2018). Allopathic Medicine and Effectiveness of Protease Inhibitors in HIV/AIDS Survival (unpublished doctoral dissertation).

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