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Transforming HIV Care: The Power Of Antiretroviral Drugs

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The management of HIV has transformed significantly with the advent of antiretroviral therapy (ART), turning HIV from a fatal disease into a controllable chronic condition. This review highlights the efficacy, safety, and advancements linked to different antiretroviral drugs used in HIV therapy. It analyzes the contributions of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs) in attaining viral suppression, boosting immune function, and improving long-term health outcomes. Findings indicate that combination regimens—particularly those including dolutegravir, bictegravir, and tenofovir alafenamide (TAF)—provide superior effectiveness and better safety profiles compared to earlier treatments. Moreover, long-acting injectable options such as cabotegravir and rilpivirine are emerging as strong alternatives to daily oral therapy, supporting improved patient adherence. Future studies are focused on advancing ART with more potent, tolerable, and durable medications to maximize treatment success and further reduce HIV transmission rates.

Keywords: Antiretroviral therapy; Life-threatening illness; HIV; Transcriptase; Safety.

HIV causes AIDS by attacking CD4 T cells, weakening the immune system and increasing susceptibility to infections and cancers. It spreads through blood, semen, bodily fluids, and breast milk, and likely originated from chimpanzees in West Africa. Two main strains exist—HIV-1 (most common) and HIV-2. The disease progresses in three stages: acute, chronic, and AIDS. Diagnosis involves rapid or self-tests, but confirmatory testing is needed due to a window period of about 28 days before antibodies become detectable. Prevention includes condoms, regular testing, male circumcision, and harm reduction strategies. Antiretroviral therapy (ART) is essential for both prevention and treatment. Pregnant women with HIV should begin ART early to prevent mother-to-child transmission.[1]

The FDA approved *zidovudine*, a nucleoside reverse transcriptase inhibitor, as the first treatment for HIV, as noted by Kemnic TR and Gulick PG in their work on HIV Antiretroviral Therapy. Antiretroviral therapy (ART), recommended by the WHO and U.S. health authorities, involves taking a combination of three drugs from at least two different classes daily. This regimen reduces HIV transmission, hospitalizations, and mortality by 60–80%, turning HIV into a manageable chronic condition. ART

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typically includes drugs from six classes, such as nnrtis, protease inhibitors, integrase inhibitors, and nrtis. Treatment has advanced from early monotherapy to highly active antiretroviral therapy (HAART). The CDC's 90-90-90 initiative aims to end the HIV epidemic by 2030.[2] The approval of zidovudine (AZT) marked a major breakthrough in HIV treatment, leading to the development of safer and more effective drugs. Today, combination antiretroviral therapy (cart) is the standard, using multiple drug classes that target different stages of HIV replication. Key drug classes include INSTIs, PIs, NNRTIs, and NRTIs. These advancements have greatly improved viral suppression, reduced illness, and extended the life expectancy of people living with HIV.[3] When a person contracts HIV and does not receive treatment, the infection progresses through three stages. For anyone who may have been exposed to HIV, it is important to talk with a healthcare professional for advice and ask them about a preventive therapy called postexposure prophylaxis (PEP), Trusted Source. People at risk of exposure to HIV can take preexposure prophylaxis (prep) [4] Trusted Source regularly to prevent the infection from taking hold, even if exposure occurs. The stages of HIV are as follows: HIV progresses through three stages:

1. Acute HIV Infection: Occurs 2–4 weeks after exposure, with flu-like symptoms in some individuals. The virus spreads rapidly by attacking CD4+ T cells and becomes irreversible once it enters+ the body.
2. Chronic HIV Infection (Clinical Latency): The virus remains active but replicates slowly. Many people show no symptoms, though HIV is still transmissible during this stage.
3. Advanced HIV (AIDS): Without treatment, this stage can last over a decade. Symptoms include night sweats, persistent cough, frequent infections, weight loss, and diarrhoea. Modern ART can stop disease progression and reduce viral load significantly.[5]

Antiretroviral therapy (ART) disrupts viral replication, helping preserve immune function. A study from 1995 to 2030 evaluates the societal and financial benefits of ART expansion compared to a scenario without ART or with limited treatment coverage.[6] The primary goals of antiretroviral therapy are to halt HIV replication by achieving and maintaining plasma viremia suppression below the detection limits of current tests; improving overall immune function, as indicated by increased CD4+ T cell counts[7]; prolonging life; reducing HIV-related morbidity; enhancing overall quality of life; and decreasing the risk of HIV transmission to others.[8] Updated guidelines recommend that all adults diagnosed with HIV start antiretroviral therapy (ART) immediately, regardless of CD4 count, to prevent disease progression, improve outcomes, and reduce transmission. This is supported by major clinical trials. Newer ART drugs offer improved potency, safety, and ease of use, allowing for lifelong viral suppression and reduced resistance. ART also plays a key public health role by preventing HIV spread. Additionally, ART-based strategies like pre-exposure prophylaxis (prep) and post-exposure prophylaxis (PEP) effectively prevent HIV in high-risk individuals.[9]

Drugs used in Antiretroviral therapy

The safety and effectiveness of *abacavir* for treating HIV in children and adolescents have been evaluated, focusing on its antiviral efficacy, potential hypersensitivity reactions, and cardiovascular risks. Data derived from four studies involving a total of 10,595 participants, which included two clinical trials and two cohort studies, indicated no significant differences in safety profiles, rates of viral suppression, or mortality between *abacavir* and other treatment options after a duration of 48 weeks. However, one particular study noted that *abacavir* resulted in enhanced viral suppression over five years. Cohort studies suggested that *abacavir* might demonstrate reduced effectiveness when used in specific therapy combinations, such as with *lopinavir*/*ritonavir* and *efavirenz*, where *stavudine* appeared to provide better efficacy. Nevertheless, the overall evidence suggests that *abacavir* remains comparable to other first-line HIV medications regarding safety and effectiveness for pediatric populations. The classification of evidence quality was determined to be intermediate for viral suppression outcomes and low for other assessed outcomes. The evidence supports the ongoing use of abacavir in HIV treatment for pediatric patients. The evidence supports the ongoing use of *abacavir* in HIV treatment for pediatric patients. Although certain combinations of therapies may produce superior results, *abacavir* continues to be a valid choice

that offers long-term advantages in achieving viral suppression. Additional research could enhance treatment approaches to improve outcomes for particular patient populations.[10] The study assessed the efficacy of *dolutegravir*, administered once daily in combination with *abacavir* and *lamivudine* (DTG–ABC–3TC), as a first-line treatment for HIV-1 infection. This randomized, double-blind trial involved 833 adult participants who were all HIV-positive and had not previously received treatment. The research compared the DTG–ABC–3TC regimen to an *efavirenz* based therapy (EFV–TDF–FTC). Over a period of 48 weeks, participants were evaluated for viral suppression (defined as fewer than 50 copies/ml), increases in CD4+ T-cell counts, safety profiles, and the emergence of drug resistance. The findings revealed that 88% of individuals in the DTG–ABC–3TC group achieved viral suppression, surpassing the 81% observed in the EFV–TDF–FTC group (P=0.003). Additionally, those receiving *dolutegravir*-based therapy experienced greater increases in CD4+ T-cell counts (267 cells/mm³ compared to 208 cells/mm³, P<0.001) and reached viral suppression more rapidly (28 days versus 84 days, P<0.001). The group receiving EFV–TDF–FTC reported a higher incidence of neuropsychiatric symptoms and rashes, whereas the DTG–ABC–3TC group had a lower rate of treatment discontinuation due to side effects (2% compared to 10%). However, insomnia was more commonly reported among those in the *dolutegravir* group. Importantly, resistance mutations were found in the EFV–TDF–FTC group but were not present in the *dolutegravir* group. Overall, *dolutegravir* combined with *abacavir* and *lamivudine* showed better efficacy and safety compared to the *efavirenz* based regimen, positioning it as a promising alternative for HIV treatment.[11]

Integrase strand transfer inhibitors (instis) represent a significant advancement in the treatment of HIV-1, with *raltegravir* being the first drug introduced in this category. *Raltegravir* has demonstrated high efficacy and good tolerability in both treatment-naive and treatment-experienced patients, achieving durable viral suppression, especially among individuals with multidrug resistant HIV. However, resistance can develop due to mutations in the integrase enzyme, which may restrict the effectiveness of *raltegravir*. To address this issue, newer second-generation instis like S/GSK1349572 are under development and show potential as effective and safer alternatives. These medications offer a novel mechanism of action, enhancing their value in contemporary HIV therapy. Clinical trials have shown that *raltegravir* may be beneficial for early treatment approaches, especially in patients with co-existing health conditions where the long-term side effects of alternative HIV medications could be problematic. Although additional research is necessary to evaluate its long-term safety, applicability in specific populations, and effectiveness in post-exposure prophylaxis, integrase strand transfer inhibitors (instis) represent a significant advancement in the management of HIV.[12] The efficacy of *tenofovir disoproxil fumarate* (*TDF*) in managing hepatitis B virus (HBV) in individuals co-infected with HIV-1 and HBV is notable. Co-infection with HIV and HBV considerably heightens the risk of advancing liver disease. Although *lamivudine* is effective against both viruses, it frequently results in the development of resistance mutations in HBV. The study evaluated the effectiveness of *TDF* through two phase 3 trials involving both antiretroviral-experienced patients (study 907) and therapy-naive patients (study 903). In study 907, *TDF* led to a reduction in HBV DNA levels by 4.9 log € after 24 weeks, whereas the placebo group experienced an increase of 1.2 log € (P=0.041). The drug demonstrated efficacy against both wild-type HBV and *lamivudine* resistant strains. In study 903, after 48 weeks, patients treated with *TDF* alongside *lamivudine* exhibited a more significant decrease in HBV DNA levels (4.7 log €) compared to those receiving only *lamivudine*, who had a reduction of 3.0 log € (P=0.055). Additionally, resistance mutations were observed in the *lamivudine* only cohort. These results affirm the robust anti-HBV efficacy of TDF in both treatment-experienced and naive populations, reinforcing its position as a viable option for managing HBV in individuals co-infected with HIV.[13]

Adrian S. Ray et al. Discuss *Tenofovir alafenamide* (*TAF*), an advanced prodrug of *tenofovir* (*TFV*) that enhances HIV treatment by providing significantly improved safety and efficacy compared to *tenofovir disoproxil fumarate (TDF)*. *TDF* has been associated with kidney issues and loss of bone mineral density due to

elevated systemic TFV levels; in contrast, TAF achieves much higher intracellular concentrations of the active metabolite, *TFV diphosphate*, while requiring substantially lower doses. With nearly 90% reduced systemic *TFV* exposure, *TAF* presents a more favorable safety profile, minimizing the risk of kidney and bone-related complications. Its enhanced stability and targeted activation make it particularly suitable for long-term HIV therapy, especially for older patients and those with pre-existing health conditions.[14] *Laura Waters* and colleagues evaluate the evidence for using *tenofovir disoproxil fumarate* (*TDF*) and *lamivudine* (3TC) as the nucleoside backbone in HIV treatment. The review discusses significant clinical trials that compare the efficacy, safety, and resistance profiles of 3TC with *emtricitabine* (FTC), as well as their use alongside *tenofovir* prodrugs, *TDF* and *tenofovir alafenamide* (*TAF*). Furthermore, it outlines international treatment guidelines regarding triple-drug and emerging dual-drug regimens. The findings affirm the therapeutic equivalence of 3TC and FTC, especially when combined with *TDF*, thereby reinforcing its effectiveness as a component of antiretroviral therapy.[15]

A multicenter, double blind clinical trial was conducted to evaluate the efficacy and safety of *zidovudine*, *didanosine*, and their combination in treating symptomatic HIV-infected children. This study involved 831 children aged between 3 months and 18 years, the majority of whom were perinatally infected and had not received antiretroviral therapy prior to the trial. Participants were categorized by age (under or over 30 months) and randomly assigned to receive either *zidovudine* alone, *didanosine* alone, or a combination of both medications. An interim analysis indicated that children treated with *zidovudine* alone faced a significantly greater risk of disease progression or death compared to those receiving combination therapy (relative risk: 0.61; P = 0.007), leading to the early discontinuation of the *zidovudine* only group. After a median follow-up period of 32 months, findings revealed that *didanosine* alone demonstrated similar efficacy to the combination therapy (relative risk: 0.98; P = 0.91), while also resulting in fewer hematologic side effects, such as anemia and neutropenia (P = 0.036).The findings indicate that both *didanosine* used alone and in combination therapy are more effective than *zidovudine* alone in delaying disease progression and lowering mortality rates in children infected with HIV. Furthermore, *didanosine* alone presents an advantage by reducing hematologic toxicity, making it a suitable alternative to combination therapy. This study underscores the necessity of optimizing antiretroviral treatment regimens for HIV-positive children to enhance survival while minimizing side effects related to treatment. Additional research is required to investigate long-term outcomes and possible resistance patterns linked to these therapies.[16] The study assessed the effectiveness and safety of combining *lamivudine* with *zidovudine* in comparison to administering either medication alone in HIV-positive individuals with CD4+ counts ranging from 200 to 500 cells per cubic millimeter. A total of 366 participants, primarily with minimal or no previous exposure to *zidovudine*, were randomly assigned to one of four treatment groups: *lamivudine* only, *zidovudine* only, or one of two dosages of the *lamivudine-zidovudine* combination. The trial was conducted in a double-blind fashion for 24 weeks, followed by an optional extension phase lasting an additional 28 weeks. The results indicated that using a combination therapy significantly enhanced immune function and lowered HIV-1 levels more effectively than monotherapy. During the first 24 weeks, patients treated with both medications showed greater increases in CD4+ cell counts and higher percentages of CD4+ cells, along with more pronounced reductions in HIV-1 RNA levels compared to those receiving either *zidovudine* or *lamivudine* alone. These beneficial effects were maintained for up to 52 weeks. Furthermore, the combination therapy was well tolerated, showing no significant rise in adverse events when compared to zidovudine monotherapy.[17]

The study involved 97 HIV-infected patients with moderate immune function (50–400 CD4 cells/mm³) and high viral loads (e”20,000 copies of HIV RNA/ml), who were randomly assigned to one of three treatment regimens for up to 52 weeks. The primary objectives were to assess viral load suppression, changes in CD4 cell counts, and adverse effects to evaluate the benefits of combining indinavir with other antiretroviral drugs. After 24 weeks, 90% of patients treated with all three drugs achieved HIV RNA levels below 500

copies/ml, in contrast to only 43% in the indinavir-only group and none in the *zidovudine-lamivudine* group. Additionally, CD4 cell counts showed a more significant increase in the groups receiving *indinavir* compared to the *zidovudine-lamivudine* group, with these enhancements sustained for up to 52 weeks. All treatment regimens were generally well tolerated, with no significant increase in adverse effects noted. The results confirm that the combination therapy of *indinavir, zidovudine*, and *lamivudine* provides superior and sustained viral suppression, making it an effective treatment strategy for HIV-infected individuals who have previously been exposed to antiretroviral therapy. This study emphasizes the critical role of protease inhibitors in combination regimens and underscores the long-term advantages of intensified therapy in managing HIV progression.[18] The effectiveness and safety of three different HIV-1 treatment regimens, emphasizing the role of the nonnucleoside reverse-transcriptase inhibitor *efavirenz*. A total of 450 treatment-naïve patients, who had not previously received lamivudine, nonnucleoside reverse-transcriptase inhibitors, or protease inhibitors, were randomly assigned to one of three regimens: efavirenz combined with *zidovudine* and *lamivudine, indinavir* with *zidovudine* and *lamivudine,* or *efavirenz* paired with indinavir. The objective was to assess the comparative efficacy and tolerability of these combinations in patients beginning HIV treatment, particularly focusing on *efavirenz*'s potential to enhance therapeutic outcomes. The findings underscore the enhanced antiviral effectiveness and tolerability of the regimen that includes *efavirenz.* The combination of *efavirenz, zidovudine*, and l*amivudine* delivers more robust and sustainable viral suppression while reducing the likelihood of treatment discontinuation due to side effects. This evidence supports the recommendation of *efavirenz*-containing regimens as a preferred first-line therapy for HIV-1 infection, providing patients with a more effective and manageable treatment alternative.[19]

A total of 302 HIV-infected patients, with CD4 counts between 50 and 300 cells/mm³ and who had been on *zidovudine* for an average of 27 months, were randomly assigned to one of three treatment groups in a study designed to assess the safety and effectiveness of *saquinavir,* an HIV protease inhibitor. The treatment groups included *saquinavir* combined with *zidovudine* and *zalcitabine*, *saquinavir* paired with *zidovudine* alone, or a regimen consisting solely of *zidovudine* and *zalcitabine*. The study was conducted over a period of 24 weeks, with an optional extension lasting between 12 to 32 weeks, to evaluate whether the addition of *saquinavir* could enhance treatment outcomes compared to a two-drug nucleoside regimen without it. The research indicated that the combination therapy involving *saquinavir, zidovudine*, and *zalcitabine* yielded greater clinical advantages compared to regimens with only two drugs. Patients who were treated with this triple therapy showed more significant increases in CD4 cell counts, substantial reductions in plasma HIV levels, and notable decreases in serum activation markers like neopterin and beta2-microglobulin. Furthermore, the addition of saquinavir did not result in a significant rise in adverse effects, demonstrating that the combination treatment was both effective and well-tolerated. Importantly, 96% of participants completed the 24-week study, reflecting strong adherence to and acceptance of the treatment.

The safety and effectiveness of *zidovudine, zalcitabine*, and their combination in treating advanced HIV. Conducted as a randomized, double-blind, controlled trial at AIDS Clinical Trials units and National Hemophilia Foundation sites, it involved 1001 participants suffering from advanced HIV disease. These patients had low CD4 counts—300 cells/mm³ or fewer if symptomatic or 200 cells/mm³ or fewer if asymptomatic—and had been receiving *zidovudine* therapy for a minimum of six months before enrollment. Participants were randomly assigned to one of three treatment groups: one group received *zidovudine* alone (600 mg/day), another group received zalcitabine alone (2.25 mg/day), and the third group was given a combination of both medications. The primary objective was to evaluate the time until disease progression or death occurred in each treatment group. Over a median follow-up period of 17.7 months, the study indicated that there was no significant overall difference in the 12-month event-free survival rates among the three treatment groups: *zidovudine* at 70%, *zalcitabine* at 67%, and combination therapy at 73% ($P = 0.26$). However, for patients with CD4 counts of 150 cells/mm³

or higher, combination therapy demonstrated a significant advantage over *zidovudine* alone, resulting in a reduced risk of disease progression or death (relative risk, 0.51; P = 0.029). Conversely, no significant differences were found among the treatment groups for patients with lower CD4 counts (50–150 cells/mm³ or fewer than 50 cells/mm³). Patients with higher CD4 counts experienced fewer severe side effects; however, *zalcitabine* used alone did not show significant advantages. These results indicate that although *zidovudine* continues to be a crucial treatment option, combining it with *zalcitabine* could be beneficial for patients who have relatively higher CD4 counts. Additional research is necessary to establish long-term benefits and the best treatment strategies.[21] This multicenter, open-label study assessed the efficacy and safety of didanosine and zalcitabine as second-line therapies for HIV-infected individuals who had previously undergone treatment with *zidovudine.* A total of 467 participants, all with CD4 cell counts of 300 or fewer per cubic millimeter or a diagnosis of AIDS, were randomly assigned to receive either *didanosine* (500 mg daily) or zalcitabine (2.25 mg daily). The primary objective was to identify which of the two nucleoside analogs was more effective in slowing disease progression and enhancing survival rates in patients with advanced HIV. After a median follow-up period of 16 months, disease progression or mortality was observed in 157 out of 230 patients receiving *didanosine,* compared to 152 out of 237 patients on *zalcitabine.* The relative risk of disease progression or death was marginally lower in the *zalcitabine* cohort than in the *didanosin*e cohort (0.93, P = 0.56), improving to 0.84 (P = 0.15) after adjusting for baseline variables such as CD4 count, Karnofsky score, and AIDS diagnosis. Importantly, the *zalcitabine* group experienced fewer deaths (88) compared to the *didanosine* group (100), with an adjusted relative risk of 0.63 (P = 0.003), indicating a potential survival advantage for *citabinzale*. Both treatment regimens exhibited comparable overall safety profiles, with adverse events reported in 66% of participants. However, peripheral neuropathy and stomatitis were more prevalent in the *zalcitabine* group, while diarrhea and abdominal pain were more commonly reported among those receiving didanosine. The study concluded that zalcitabine was at least as effective as *didanosine* in delaying disease progression and mortality in patients who had not responded to *zidovudine* therapy. Although both medications presented unique side effect profiles, z*alcitabine* appeared to offer a potential benefit in terms of survival.[22]

This randomized controlled trial aimed to determine if combining zidovudine with either *zalcitabine* or *didanosine* could inhibit the development of *zidovudine*-resistant HIV in patients with advanced HIV infection. The study involved HIV-1-infected individuals who had fewer than 300 CD4 cells per cubic millimeter and had received less than four weeks of zidovudine treatment prior to enrollment. Participants were randomly assigned to one of three treatment groups: z*idovudine* alone, *zidovudine* with *zalcitabine,* or z*idovudine* with *didanosine*. The findings revealed that combination therapy did not effectively prevent the emergence of zidovudine resistance. Nevertheless, those receiving combination therapy demonstrated significant immunologic and virologic improvements compared to patients on zidovudine monotherapy. Over a 72-week period, the increase in CD4 cell counts was more pronounced in the combination therapy groups, and there were greater and more sustained reductions in serum HIV-1 RNA levels. Alth ough the study was not structured as a clinical endpoint trial, patients treated with *zidovudine* and *didanosine* experienced a significant delay in the onset of the first AIDS-defining event or death compared to those receiving zidovudine alone. These results indicate that while *zidovudine* resistance continues to pose a challenge, combination therapy offers substantial virologic and immunologic benefits, reinforcing the importance of combination antiretroviral therapy in the management of HIV.[23] This randomized controlled trial aimed to determine if combining *zidovudine* with either *zalcitabine* or *didanosine* could inhibit the development of *zidovudine*-resistant HIV in patients with advanced HIV infection. The study involved HIV-1-infected individuals who had fewer than 300 CD4 cells per cubic millimeter and had received less than four weeks of *zidovudine* treatment prior to enrollment. Participants were randomly assigned to one of three treatment groups: *zidovudine* alone, zidovudine with *zalcitabine,* or *zidovudine* with didanosine. The findings revealed that combination therapy did not effectively

Table 1. Patents and Marketed products of Antiretroviral drugs for HIV Treatment

Drug name	Inventors	FDA ap-proval date	Patent no	Brand name
Abacavir [34]	Jorge Medrano Rupé-rez Julio Campon Pardo Laia Elías Rius Ramón Berenguer Maimó	Dec 17 1998	EP1857458A1	Ziagen
Emtricitabine [35]	Srinivas simhadriv-enkata Sunil Kumar indukuriseeta Raman-janeyulu gorantlaven-kateswara Rao golla-pallinagireddy ARI-KATLA	July 2 2003	US7534885B2	Emtriva
Lamivudine [36]	Bandi Parthasaradhi reddymale Srinivas reddypothireddy Ven-kateswar reddymup -pidi Vanaja Kumari	Nov 17 1995	US8481554B2	Epivir
Tenofovir disoproxil Fumarate [37]	Debashish dattasiva Rama Prasad vel-lankiarabinda sahuraja Babu balusumastan Rao ravihari Babu nandipatishankar ra-malakshmana Rao vadalisrikanth Sarat Chandra gorant-lasrinivasa Rao da-sarinagaraju Mittapelly	Oct 26 2001	C07F9/65616	Viread
Zidovudine [38]	Bruno Konrad rada-tuskhashayar Karimian	March 19 1987	EP0550714B1	Retrovir
Doravirine [39]	Santipharp pan-maiaditya tatavartian-drew M. Farrington-varsha biyyalaleonar-do R. Allainmarcela nefliugerard R. Klinzingjie ren-matthew Lamm	August 30 2018	US10603282B2	Pefeltro
Efavirenz [40]	Udit batraraymond J. Higginskaren C. Thompsonashok V. Katdare	Sept 17 1998	WO199961026A1	Sustiva
Etravirine [41]	Dong liangmathew Kizhakkekara jo-sephjyothy johncyril V Abobo	Jan 18 2008	US8703786B2	Intelence
Nevirapine [42]	Saeed ahmadfrank guptonjenson verghesestyler MCQUADE	June 21 1996 March 25 2011	WO2016118586A1	Viramune Viramune XR
Rilpivirine [43]	Bandi Parthasaradhi reddykura Rathnakar reddydasari Murali-dhara reddyadulla Venkat Narsimha red-dybandi Vamsi Krish-na	May 20 2011 March 15 2024	US9233935B2	Edurant Edurant PED
Stavudine [44]	Purna Chandra rayjagan Mohana Chary tummanapal-liseeta Ramanjaneyulu Gorantla	June 27 1994	US8026356B2	Zerit
Zalcitabine [45]	Zhang Hao	June 19 1992	CN102512387B	Dideoxycyti-dine
Didanosine [46]	Ismat ullahgary J. Wiley	Oct 9 1991	EP1098635B1	Videx EC
Delaviridine [47]	Alice C. Martinoash-ley H. Bateswalter morozowiche. John Lee	1997	EP1083885B1	Rescripter
Saquinavir [48]	Ogari Pacheco Elisa russovalter Russo	Dec 7 1995	US20060217320A1	Invirase
Indinavir [49]	Yongku sunfrank P. Gortsemacarl le-blondkai Rossen	March 13 1991	US5981759A	Crixivan
Nelfinavir [50]	Chava Satyanarayana Vasireddy Umamahe-swara-raovellanki Siva Ram prasadbalusu Rajababu	March 1997	US8367832B2	Viracept
Amprenavir [51]	John J. Talley	Apr 15 1995	LU90736I2	Agenerase, glax-osmithkline
Fosamprenavir [52]	Surinder Kumar aro-rasamir Shanteshwar shabadegaurav ku-marpurna Chandra raygirij Pal Singh	Oct 10 2003	WO2012032389A2	Lexiva
Ritonavir [53]	Bandi parthasaradhip-odili khadgapathigoli Kamalakar Reddy	March 1, 1996	US20150045400A1	Norvir
Lopinavir [54]	Hou Pengyi Belov Yevgeny	Sept 15 2000	CN110903249A	Kaletra
Atazanavir [55]	Anup Avijit choudhuryashish jaiswalkhalid rafirajeev Raghuvanshi	Jun 202003	US20120121722A1	Reyataz
Enfuvirtide [56]	Ananda kuppan-namaria Bhaskar Red-dy Komma red-dydebashish Datta	Mar 13 2003	WO2011095989A2	Fuzeon

prevent the emergence of *zidovudine* resistance. Nevertheless, those receiving combination therapy demonstrated significant immunologic and virologic improvements compared to patients on *zidovudine* monotherapy. Over 72 weeks, the increase in CD4 cell counts was more pronounced in the combination therapy groups, and there were greater and more sustained reductions in serum HIV-1 RNA levels. Although the study was not structured as a clinical endpoint trial, patients treated with *zidovudine* and *didanosine* experienced a significant delay in the onset of the first AIDS-defining event or death compared to those receiving *zidovudine* alone. These results indicate that while *zidovudine* resistance continues to pose a challenge, combination therapy offers substantial virologic and immunologic benefits, reinforcing the importance of combination antiretroviral therapy in the management of HIV.[24]

This study examines the characteristics, effectiveness, and clinical uses of emtricitabine (FTC), a nucleoside reverse transcriptase inhibitor (NRTI) that targets both HIV and hepatitis B virus (HBV). Emtricitabine exhibits many similarities to lamivudine (3TC) regarding antiviral effectiveness, safety, and resistance profiles. Notably, FTC has a longer intracellular half-life, which facilitates once-daily dosing, potentially enhancing patient adherence. Clinical trials have shown that FTC is comparable to 3TC when included in a triple-drug regimen for HIV treatment. Furthermore, research comparing FTC to stavudine indicates that FTC is more effective and better tolerated. Although FTC is not officially sanctioned for HBV treatment, it is commonly utilized in patients who are co-infected with HIV and HBV, particularly in conjunction with tenofovir, another antiviral that acts against both viruses. Current treatment guidelines from the International AIDS Society–USA and the US Department of Health and Human Services endorse the use of FTC in combination with *tenofovir, didanosine, or zidovudine* as a preferred nucleoside backbone regimen for individuals undergoing antiretroviral therapy. The choice between FTC and 3TC often hinges on the specific drug formulations and combinations available in various treatment regimens. In conclusion, emtricitabine is a highly tolerated and effective antiretroviral medication that offers benefits in dosing convenience and efficacy against both HIV and HBV. It is extensively used in combination therapies, especially in formulations with tenofovir, to enhance treatment outcomes for patients with co-infection of HIV and HBV.[25] The phase 3 randomized, double-blind study assessed the effectiveness and safety of a single-tablet treatment consisting of *elvitegravir, cobicistat, emtricitabine*, and *tenofovir disoproxil fumarate* compared to the standard treatment of *efavirenz, emtricitabine, and tenofovir* for the initial treatment of HIV infection. A total of 700 participants who had not previously received treatment were enrolled and randomly assigned to one of the two treatment groups. To qualify, participants needed to have an HIV RNA level of at least 5000 copies per milliliter and show susceptibility to efavirenz, emtricitabine, and tenofovir. The main outcome measured was the percentage of patients achieving an HIV RNA level below 50 copies per milliliter at week 48. The results showed that the elvitegravir-based regimen was not inferior to the efavirenz-based regimen, with 87.6% of patients in the elvitegravir group and 84.1% in the efavirenz group achieving viral suppression. Discontinuation rates due to side effects were similar in both groups. However, those on the efavirenz regimen reported more frequent side effects such as nausea, dizziness, abnormal dreams, insomnia, and rash. In contrast, the elvitegravir regimen was associated with more significant increases in serum creatinine levels, indicating a potential impact on kidney function. These results suggest that the single-tablet regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir is a suitable alternative to the standard efavirenz-based treatment for first-line HIV therapy. With comparable efficacy and a different safety profile, this regimen provides a convenient once-daily option that may improve treatment adherence and simplify HIV management.[26]

In phase 3 trial was a randomized, double-blind, multicenter study that evaluated the efficacy and safety of a fixed-dose combination of *bictegravir, emtricitabine, and tenofovir alafenamide* against a regimen of *dolutegravir* combined with *emtricitabine and tenofovir alafenamide* for the initial treatment of HIV-1 infection. Conducted at 126 outpatient centers across 10 countries, the study enrolled treatment-naive adults who had an HIV-1 RNA level of at least 500 copies per milliliter and an estimated glomerular filtration rate of no less than 30

milliliters per minute. The trial also included participants co-infected with chronic hepatitis B or C. Patients were randomly assigned in a 1:1 ratio to receive either the single-tablet regimen of *bictegravir, emtricitabine*, and *tenofovir alafenamide or dolutegravir* along with the same nucleoside/nucleotide backbone. The primary endpoint was to determine the proportion of participants achieving HIV-1 RNA levels below 50 copies per milliliter at week 48, with a predefined non-inferiority margin set at –12%. A total of 742 individuals underwent screening, with 657 of them randomly assigned to receive treatment; among these, 327 were given a *bictegravir*-based regimen and 330 received a *dolutegravir*-based regimen. At the 48-week mark, viral suppression was observed in 89% of patients on the *bictegravir* regimen and in 93% of those on the *dolutegravir* regimen. The difference of –3.5% (with a 95% confidence interval ranging from –7.9 to 1.0 and a p-value of 0.12) confirmed that the *bictegravir* regimen was non-inferior. Importantly, no participants in either group developed resistance to the medications being studied. Both regimens exhibited similar safety profiles; however, adverse events related to the study drug occurred significantly less frequently in the *bictegravir* group (18%) compared to the dolutegravir group (26%, p=0.022). Treatment discontinuation due to adverse events was minimal across both groups.[27]

The advance trial evaluated the effectiveness and safety of three first-line antiretroviral treatment regimens for HIV over a duration of 96 weeks. The study focused on comparing (1) dolutegravir combined with *emtricitabine* and *tenofovir alafenamide*, (2) *dolutegravir* paired with *emtricitabine and tenofovir disoproxil fumarate*, and (3) ef*avirenz* with *emtricitabine and tenofovir disoproxil fumarate*, the latter of which was previously endorsed by the World Health Organization. This phase 3, open-label, non-inferiority trial took place in Johannesburg, South Africa, and involved participants recruited from 11 public health clinics. To qualify for the study, participants had to be at least 12 years old, have an HIV-1 RNA level of 500 copies per milliliter or higher, weigh a minimum of 40 kilograms, and not have received antiretroviral therapy in the six months prior. Those with tuberculosis or who were pregnant were excluded from participation. Ultimately, 1,053 participants were randomly assigned in a 1:1:1 ratio to one of the three treatment regimens. The primary efficacy endpoint—suppressing HIV-1 RNA to below 50 copies per milliliter at 48 weeks—has been previously reported. This analysis, however, concentrated on the secondary endpoint of viral suppression at week 96, along with safety outcomes. The findings indicated that all three treatment regimens successfully suppressed HIV at week 96, showing no significant differences among them. Dolutegravir-based regimens were found to be non-inferior to the *efavirenz*-based regimen. In terms of safety, the groups receiving *tenofovir alafenamide* exhibited better preservation of bone mineral density and renal function compared to those treated with *tenofovir disoproxil fumarate*. Nonetheless, the occurrence of specific adverse events differed across the treatment groups. At the 96-week mark, *dolutegravir*-based regimens, whether combined with *tenofovir alafenamide* or *tenofovir disoproxil fumarate,* demonstrated comparable effectiveness to the *efavirenz*-based regimen in achieving viral suppression, while also presenting more favorable safety profiles. These results further endorse *dolutegravir*-based therapies as the preferred first-line options for treating HIV infection.[28]

Two phase 3, double-blind, randomized studies were carried out to evaluate the efficacy and safety of *tenofovir alafenamide* (*TAF*) compared to *tenofovir disoproxil fumarate (TDF*) when combined with *elvitegravir*, *cobicistat*, and *emtricitabine* (*E/C/F*). The objective of these studies was to determine if TAF, a new prodrug of tenofovir that results in lower plasma concentrations, could mitigate the renal and bone toxicity linked to TDF while preserving comparable antiviral effectiveness .The trials included treatment-naive HIV-infected individuals from 178 sites across 16 countries, specifically selecting those with an estimated creatinine clearance of at least 50 ml/min. Participants were randomly assigned in a 1:1 ratio to receive either E/C/F/TAF or E/C/F/TDF, along with a matching placebo, and were monitored for 48 weeks. The primary outcome measure was the percentage of patients achieving plasma HIV-1 RNA levels below 50 copies per milliliter, with a non-inferiority margin set at 12%. Furthermore, renal and bone safety indicators were evaluated

to assess the advantages of TAF over TDF. Out of 2,175 patients screened, 1,744 were randomized, and 1,733 received treatment (866 in the E/C/F/TAF group and 867 in the E/C/F/TDF group). By week 48, virological suppression was observed in 92% of patients on E/C/F/TAF and 90% on E/C/F/TDF, confirming non-inferiority (adjusted difference: 2.0%; 95% CI –0.7 to 4.7). Notably, E/C/F/TAF showed significantly improved renal and bone safety results. Patients receiving TAF experienced smaller increases in serum creatinine (0.08 vs. 0.12 mg/dl; $p<0.0001$), lower levels of proteinuria (–3% vs. 20%; $p<0.0001$), and less bone mineral density loss at the spine (–1.30% vs. –2.86%; $p<0.0001$) and hip (–0.66% vs. –2.95%; $p<0.0001$).[29]

A phase 3, double-blind, randomized, non-inferiority trial was carried out to assess the efficacy and safety of a single-tablet regimen consisting of *elvitegravir* (*EVG*), *cobicistat* (*COBI*), *emtricitabine* (*FTC*), and *tenofovir disoproxil fumarate (TDF) (EVG/COBI/FTC/TDF)* in comparison to a *ritonavir*-boosted protease inhibitor regimen featuring atazanavir (ATV) with ritonavir (RTV), along with *FTC/TDF (ATV/RTV+FTC/TDF)*. The objective of the study was to determine if the integrase strand transfer inhibitor (INSTI)-based single-tablet regimen could be a viable option for initial treatment of HIV-1. The trial included treatment-naive patients with HIV-1 RNA levels of at least 5000 copies/ml and confirmed susceptibility to *atazanavir*, *emtricitabine*, and *tenofovir*. Participants were randomly assigned in a 1:1 ratio to receive either EVG/COBI/FTC/TDF or ATV/RTV+FTC/TDF, both accompanied by matching placebos. Randomization was conducted using a computer-generated method, ensuring that treatment assignments were concealed from patients, investigators, and study personnel. The primary endpoint was the percentage of patients achieving HIV-1 RNA levels of 50 copies/ml or lower at week 48, evaluated using the FDA snapshot algorithm with a non-inferiority margin set at 12%. A total of 715 patients participated in the study, with 708 receiving treatments—353 in the EVG/COBI/FTC/TDF group and 355 in the ATV/RTV+FTC/TDF group. By week 48, 89.5% of patients on EVG/COBI/FTC/TDF achieved virological suppression, compared to 86.8% in the ATV/RTV+FTC/TDF group, demonstrating non-inferiority (adjusted difference: 3.0%; 95% CI: –1.9% to 7.8%). Both treatment regimens were well-tolerated, showing similar rates of discontinuation due to adverse events (3.7% versus 5.1%). Patients receiving EVG/COBI/FTC/TDF experienced fewer abnormal liver function test results and significantly lower increases in fasting triglycerides (90 µmol/L compared to 260 µmol/L; $p=0.006$). Changes in serum creatinine levels and estimated glomerular filtration rates were minimal in both groups, stabilizing by week 8.[30]

Bictegravir is an integrase strand transfer inhibitor (INSTI) known for its robust resistance barrier, making it a compelling choice for HIV therapy. It is combined with emtricitabine and *tenofovir alafenamide (AF*) in a single-tablet regimen called Biktarvy. Clinical trials have shown that Biktarvy is equally effective as other standard HIV treatment regimens in achieving and sustaining viral suppression. This combination is well-tolerated and does not necessitate genetic testing before starting treatment. Biktarvy is particularly advantageous for patients who are co-infected with hepatitis B (HBV), as both *emtricitabine* and *tenofovir alafenamide* are effective against HBV. Furthermore, it is a suitable treatment option for individuals with moderate renal impairment, as it can be administered to patients with a creatinine clearance of at least 30 ml/min. Although additional research on its cost-effectiveness is warranted, Biktarvy® offers a convenient and effective treatment alternative for both treatment-naive and experienced patients, especially those with concurrent HBV or renal issues.[31]

The study investigated the effectiveness of transitioning HIV treatment from *zidovudine* to *didanosine* in patients with advanced or asymptomatic HIV infection. Although zidovudine is a proven treatment, its effectiveness may decrease over time. Didanosine, another reverse transcriptase inhibitor, was considered as a potential alternative. In a multicenter, double-blind trial involving 913 participants who had been on *zidovudine* for a minimum of 16 weeks, subjects were randomly assigned to either continue with *zidovudine* (600 mg/day) or switch to *didanosine* at two different dosages (500 mg/day or 750 mg/day). The main goal was to determine if switching to *didanosine* would lead to better clinical outcomes.

The results indicated that switching to 500 mg/day of *didanosine* significantly lowered the occurrence of new AIDS-related events and deaths compared to ongoing *zidovudine* treatment (relative risk 1.39, 95% CI 1.06–1.82, P = 0.015). However, the higher dosage of 750 mg/day of *didanosine* did not show a significant benefit over *zidovudine*. Both groups receiving *didanosine* experienced increases in CD4 cell counts (P < 0.001) and reductions in p24 antigen levels (P = 0.03 for 500 mg, P = 0.005 for 750 mg).[32] The effectiveness of switching HIV treatment from *zidovudine* to *didanosine* in patients with advanced or asymptomatic HIV infection. While *zidovudine* is an effective treatment, its efficacy can diminish over time. *Didanosine*, another reverse transcriptase inhibitor, was evaluated as an alternative. In a multicenter, double-blind trial, 913 participants who had been on *zidovudine* for at least 16 weeks were randomly assigned to receive either continued zidovudine (600 mg/day) or *didanosine* at two different doses (500 mg/day or 750 mg/day). The primary objective was to assess whether switching to *didanosine* provided improved clinical outcomes. Results showed that switching to 500 mg/day of *didanosine* significantly reduced the incidence of new AIDS-defining events and deaths compared to continued *zidovudine* treatment (relative risk 1.39, 95% CI 1.06–1.82, P = 0.015). However, the higher 750 mg/day dose of *didanosine* did not provide a clear advantage over *zidovudine*. Both *didanosine* groups demonstrated increased CD4 cell counts (P < 0.001) and reductions in p24 antigen levels (P = 0.03 for 500 mg, P = 0.005 for 750 mg).The findings suggest that switching from zidovudine to 500 mg/day of didanosine slows HIV disease progression, making it a more effective treatment option for patients with advanced or asymptomatic HIV infection.[33]

DISCUSSION

Abacavir is considered comparable to other first-line HIV treatments in terms of safety and efficacy for children and adolescents despite some concerns about its effectiveness in certain therapy combinations.[57] The study found that *dolutegravir* combined with *abacavir* and *lamivudine* led to higher rates of viral suppression, greater increases in CD4+ T-cell counts, and faster viral suppression compared to *efavirenz*-based therapy over 48 weeks.[58] Instis like *raltegravir* effectively treat HIV, but resistance can occur. Newer instis are being developed to address this. *Raltegravir* is promising for early treatment, especially in patients with other health issues.[59] Tenofovir DF has shown strong anti-HBV efficacy in both treatment-experienced and naive patients, confirming its role as an effective management option for HBV in HIV-coinfected individuals..[60] The combination of *lamivudine* and *zidovudine* presents a more effective strategy for improving outcomes in HIV treatment. This dual therapy enhances immune response, markedly decreases viral load, and maintains a favorable safety profile, making it an appropriate choice for patients with limited prior exposure to antiretroviral medications. The study underscores the importance of dual therapy in optimizing HIV management and supports its integration into standard treatment guidelines. Further research may be required to investigate the long-term benefits and resistance patterns associated with this combination. Additionally, a three-drug regimen that includes *indinavir*, *zidovudine*, and *lamivudine* has proven to be significantly more effective in lowering HIV RNA levels and boosting immune function compared to indinavir alone or the combination of *zidovudine* and *lamivudine*.[61] The treatment of protocol involving *efavirenz* in conjunction with *zidovudine* and *lamivudine* was the most effective and well-tolerated among the three alternatives evaluated. At the end of the treatment duration, 70% of patients undergoing the *efavirenz-zidovudine-lamivudine* regimen reached undetectable levels of HIV RNA, compared to just 48% of those treated with the *indinavir-zidovudine-lamivudine* regimen (P < 0.001).[62] The results provide robust support for a three-drug treatment plan that incorporates saquinavir, aimed at improving antiviral efficacy, suppressing viral replication, and promoting immune recovery in individuals with HIV. While further studies are necessary to assess the long-term benefits in reducing morbidity and mortality, this trial offers compelling evidence in favor of combination therapies that include saquinavir for managing advanced HIV.[63] Both *E/C/F/TAF and E/C/F/TDF* exhibit significant virological efficacy; however, TAF offers distinct advantages for kidney and bone health. Although the studies

did not specifically focus on evaluating long-term clinical outcomes such as renal failure or fractures, the findings indicate that treatment regimens incorporating TAF may represent a safer long-term choice for individuals initiating HIV therapy.[64]

The single-tablet regimen *EVG/COBI/FTC/TDF* is a viable, non-inferior option compared to the protease inhibitor-based regimen for first-line HIV-1 treatment. With its once-daily dosing and favorable safety profile, *EVG/COBI/FTC/TDF* could simplify HIV management if it receives clinical approval.[65] The switching from zidovudine to 500 mg/day of didanosine may slow the progression of HIV disease, positioning it as a more effective treatment option for patients with advanced or asymptomatic HIV infection.[66] nrtis serve as the foundation for the majority of antiretroviral therapy (ART) regimens. Abacavir, a widely utilized NRTI, has been explored in combination therapies specifically for paediatric and adolescent populations. A systematic review and meta-analysis evaluating the effectiveness and safety of abacavir-containing regimens in these age groups indicated that combinations including abacavir were both well tolerated and effective as first-line treatments. Likewise, the pairing of dolutegravir with *abacavir-lamivudine* exhibited significant virologic suppression in adults infected with HIV-1, underscoring the regimen's durability and effectiveness.[67] *Tenofovir disoproxil fumarate (TDF*) and its newer formulation, *tenofovir alafenamide (TAF*), have been thoroughly examined for their effectiveness in both treatment-naïve and treatment-experienced individuals. Research has demonstrated that TAF, a novel prodrug, offers virologic efficacy comparable to that of TDF while presenting enhanced safety profiles concerning renal and bone health. Furthermore, TDF-based therapies have proven effective in patients co-infected with HIV-1 and hepatitis B virus (HBV), solidifying its significance as a crucial component in ART regimens.[68] *Zidovudine*, recognized as one of the first nucleoside reverse transcriptase inhibitors (nrtis), has been extensively researched in multiple combination treatment regimens. Studies comparing *zidovudine* with *didanosine* in patients suffering from advanced HIV infection revealed that transitioning to didanosine led to enhanced clinical outcomes, such as decreased disease progression and lower mortality rates. Likewise, investigations into combination therapies involving *zidovudine* alongside *zalcitabine* or *didanosine* showed superior virologic and immunologic responses when compared to zidovudine used alone.[69]

Integrase Strand Transfer Inhibitors (INSTIs) have transformed the landscape of HIV treatment by providing effective viral suppression and a robust resistance barrier. *Bictegravir*, an INSTI that is part of a single-tablet regimen with *emtricitabine* and *tenofovir alafenamide* (Biktarvy), has demonstrated significant efficacy in sustaining viral suppression while maintaining a positive safety profile. A randomized, double-blind study that compared *bictegravir*/*emtricitabine*/*TAF* to *dolutegravir* combined with *emtricitabine* and TAF showed that both treatment options were non-inferior, achieving high levels of virologic suppression.[70] *Elvitegravir*, another INSTI, has been assessed in various co-formulated regimens. Research comparing *elvitegravir/cobicistat/emtricitabine/TDF* to *efavirenz*/*emtricitabine/TDF* indicated similar efficacy, with the elvitegravir regimen resulting in fewer central nervous system-related side effects. Additionally, studies that evaluated tenofovir alafenamide against tenofovir disoproxil fumarate in conjunction with *elvitegravir*, *cobicistat*, and *emtricitabine* highlighted the enhanced renal and bone safety associated with TAF-based therapies.[71] *Dolutegravir*, a prominent INSTI, has undergone extensive investigation in various combinations. The advance trial assessed *dolutegravir* with *emtricitabine* and either *tenofovir alafenamide* or *tenofovir disoproxil fumarate* against *efavirenz*-based regimens, demonstrating superior virologic suppression and better tolerability in the dolutegravir groups.[72] Integrase Strand Transfer Inhibitors (instis) have transformed the landscape of HIV treatment by providing effective viral suppression and a robust resistance barrier. *Bictegravir*, an INSTI that is part of a single-tablet regimen with emtricitabine and tenofovir alafenamide (Biktarvy®), has demonstrated significant efficacy in sustaining viral suppression while maintaining a positive safety profile. A randomized, double-blind study that compared *bictegravir/emtricitabine/TAF* to dolutegravir combined with emtricitabine and TAF showed that both treatment options were non-inferior, achieving high levels of virologic suppression.[73] *Elvitegravir*,

another INSTI, has been assessed in various co-formulated regimens. Research comparing *elvitegravir/cobicistat/emtricitabine/TDF to efavirenz/emtricitabine/TDF* indicated similar efficacy, with the *elvitegravir* regimen resulting in fewer central nervous system-related side effects. Additionally, studies that evaluated tenofovir alafenamide against tenofovir disoproxil fumarate in conjunction with *elvitegravir*, *cobicistat*, and *emtricitabine* highlighted the enhanced renal and bone safety associated with TAF-based therapies.[74] Dolutegravir, a prominent INSTI, has undergone extensive investigation in various combinations. The ADVANCE trial assessed dolutegravir with emtricitabine and either *tenofovir alafenamide or tenofovir disoproxil fumarate* against *efavirenz*-based regimens, demonstrating superior virologic suppression and better tolerability in the dolutegravir groups. [75] Innovative Treatment Approaches and Prospective Developments as antiretroviral therapy (ART) progresses, researchers are investigating new agents that offer enhanced safety and long-lasting formulations. Regimens based on *bictegravir*, *dolutegravir*, and other integrase strand transfer inhibitors (instis) have established new standards for effectiveness and tolerability, with ongoing studies focused on further refining treatment methods. Long-acting injectable options and two-drug combinations present promising alternatives, especially for patients who prefer more straightforward dosing regimens. In summary, the reviewed studies underscore the ongoing progress in ART, highlighting the importance of personalized treatment strategies that take into account efficacy, safety, and individual patient needs.[76]

CONCLUSION

The management of HIV continues to progress, largely due to advancements in antiretroviral therapy (ART). Nucleoside reverse transcriptase inhibitors (NRTIs) remain the cornerstone of most ART regimens, with agents such as abacavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) showing strong effectiveness in different combinations. Among these, TAF provides improved renal and bone safety compared to TDF. Integrase strand transfer inhibitors (INSTIs) — including dolutegravir, bictegravir, and elvitegravir — have significantly strengthened viral suppression and raised resistance thresholds. Evidence demonstrates that dolutegravir-based therapies surpass efavirenz-based regimens in both virologic control and tolerability. Combination treatments are crucial for successful HIV therapy, and regimens like lamivudine–zidovudine and three-drug combinations featuring indinavir, efavirenz, or saquinavir have shown better immune recovery, viral suppression, and overall clinical outcomes. New therapeutic strategies are also shifting toward long-acting injectable options and simplified two-drug combinations to enhance adherence and improve patient satisfaction. Overall, this review highlights efforts to optimize ART by improving its efficacy, safety, and patient-focused delivery to ensure sustained HIV management. Future research will target the development of more potent, well-tolerated, and longer-acting agents to further enhance treatment effectiveness.

Future work

Recent progress in antiretroviral (ARV) medications has concentrated on long-acting formulations to enhance patient adherence and improve treatment results. Significant innovations include *Lenacapavir* (LEN), which is administered subcutaneously every six months, and the combination therapy of *Rilpivirine* (*RPV*) and *Cabotegravir* (*CAB*), which is given every two months, both demonstrating non-inferiority in clinical trials. *Islatravir* (*ISL*) also shows potential but has encountered challenges due to safety issues. Furthermore, new arvs such as Doravirine (DOR) exhibit unique resistance profiles with limited cross-resistance, and the latest arvs are effective against a range of HIV subtypes. The advancement of long-acting arvs and drugs resistant to certain strains is set to improve HIV treatment alternatives.[77] Recent progress in antiretroviral (ARV) medications has concentrated on long-acting formulations to enhance patient adherence and improve treatment results. Significant innovations include *Lenacapavir* (*LEN*), which is administered subcutaneously every six months, and the combination therapy of *Rilpivirine* (*RPV*) and *Cabotegravir* (*CAB*), which is given every two months, both demonstrating non-inferiority

in clinical trials. *Islatravir* (*ISL*) also shows potential but has encountered challenges due to safety issues. Furthermore, new arvs such as *Doravirine* (*DOR*) exhibit unique resistance profiles with limited cross-resistance, and the latest arvs are effective against a range of HIV subtypes. The advancement of long-acting arvs and drugs resistant to certain strains is set to improve HIV treatment alternatives.[78] A primary objective of NIAID-funded research on HIV treatment is to create long-acting therapies that, in contrast to existing antiretrovirals requiring daily administration, could be taken weekly, monthly, or even less frequently. These long-acting options may be more manageable for some individuals compared to daily pills and could also offer reduced toxicity and greater cost efficiency. The research is focusing on three categories of agents: long-acting medications, broadly neutralizing antibodies, and therapeutic vaccines.[79]

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