REVIEW

Approved HIV reverse transcriptase inhibitors in the past decade

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Abstract HIV reverse transcriptase (RT) inhibitors are the important components of highly active antiretroviral therapies (HAARTs) for anti-HIV treatment and pre-exposure prophylaxis in clinical practice. Many RT inhibitors and their combination regimens have been approved in the past ten years, but a review on their drug discovery, pharmacology, and clinical efficacy is lacking. Here, we provide a comprehensive review of RT inhibitors (tenofovir alafenamide, rilpivirine, doravirine, dapivirine, azvudine and elsvulfavirine) approved in the past decade, regarding their drug discovery, pharmacology, and clinical efficacy in randomized controlled trials. Novel RT inhibitors such as islatravir, MK-8504, MK-8507, MK8583, IQP-0528, and MIV-150 will be also highlighted. Future development may focus on the new generation of novel antiretroviral inhibitors with higher bioavailability, longer elimination half-life, more favorable side-effect profiles, fewer drug–drug interactions, and higher activities against circulating drug-resistant strains.

Keywords HIV treatment; HAART; NRTI; NNRTI; Clinical efficacy

Abbreviations: 3TC, (−)-2',3'-dideoxy-3'-thiacytidine (common name, lamivudine); ABC, abacavir; ATV, atazanavir; AZT, 3'-azido-3'-deoxy-thymidine (common name, zidovudine); BIC, bictegravir; CAB, cabotegravir; CC50, the 50% cytotoxic concentration; COBI, cobicistat; DOR, doravirine; DVP, dapivirine; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EC50, half maximal effective concentration; EFV, efavirenz; ESV, elsvulfavirine; EVG, elvitegravir; F, bioavailability; FDA, US Food and Drug Administration; FTC, (−)-2',3'-dideoxy-5-fluoro-3'-thiacytidine (common name, emtricitabine); HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IAS-USA, International Antiviral Society-USA; IC50, half maximal inhibitory concentration; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; MSM, men who have sex with men; RPV, rilpivirine; t½, elimination half-life; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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1. Introduction

In 2020, 37.7 million people were living with HIV infections according to the recent update from The Joint United Nations Programme on HIV/AIDS (www.unaids.org). Although HIV cure is still unavailable, antiretroviral therapies were accessible to 27.5 million patients living with HIV in 2020, and nearly 66% of patients living with HIV had virological suppression (www.unaids.org). Due to the large population of new cases (1.5 million) and untreated patients (10.2 million), it remains important to develop effective therapies to control HIV infections and transmission.

Highly active antiretroviral therapy (HAART) is the current standard of care for the management of HIV infections in clinical practice. To interrupt multiple steps of the HIV life cycle, HAARTs are mostly comprised of three compounds (Fig. 1), including two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), one integrase inhibitor, or one protease inhibitor (boosted by ritonavir or cobicistat)\(^1\). As shown in Fig. 2, NRTIs and NNRTIs target different binding pockets near the catalytic site of HIV reverse transcriptase (RT) to block the viral transcription of a double-stranded viral DNA genome from a single-stranded viral RNA genome\(^2^,^4^,^5^,^8\). NNRTIs can inhibit the reverse transcriptase initiation complex even during the early viral transcription\(^9\). Integrase inhibitors such as bictegravir (BIC), dolutegravir (DTG), and elvitegravir (EVI) target the catalytic site of HIV integrase to inhibit the viral integration of proviral DNA into host genomes\(^1\). Protease inhibitors such as darunavir (DRV) compete with natural substrates of HIV protease to inhibit the protease-mediated cleavage of gag and gagpol precursors\(^1\). Among these four drug classes, NRTIs are the key backbones of combination regimens according to the recent update of the International Antiviral Society-USA (IAS-USA) guidelines\(^10\), the European AIDS Clinical Society (EACS) guidelines\(^11\), the NIH HIV/AIDS guidelines (https://hivinfo.nih.gov), and the WHO guidelines on HIV/AIDS (www.who.int).

From 1987 to 2010, eight NRTIs and four NNRTIs were officially approved to combat HIV infections. In the drug class of NRTIs, the US Food and Drug Administration (FDA) approved zidovudine (AZT) in March 1987, followed by didanosine (ddI) in October 1991, zalcitabine (ddC) in June 1992, stavudine (d4T) in June 1994, lamivudine (3TC) in November 1995, abacavir (ABC) in December 1998, tenofovir disoproxil fumarate (TDF) in October 2001, and emtricitabine (FTC) in July 2003. In the drug class of NNRTIs, nevirapine (NVP), delavirdine (DLV), efavirenz (EFV), and etravirine (ETR) were approved by the FDA\(^4,^12^-^14\).

The “old” generation of the preceding RT inhibitors is often challenged by the emergence of drug resistance and adverse events. For example, (i) zalcitabine, stavudine, and delavirdine were discontinued because of severe adverse effects, inconvenient administration (three times daily), and low genetic barrier to resistance\(^1\). (ii) Zidovudine, didanosine, stavudine, and nevirapine are no longer recommended due to their toxicity, low efficacy, and severe drug resistance\(^10,^11\). (iii) Abacavir-based therapies may increase the risk of cardiovascular diseases compared with abacavir-free regimens\(^15\). (iv) Efavirenz is associated with a high incidence of neuropsychiatric complications\(^16\). (v) TDF may cause renal impairment and reduce bone mineral density\(^17\). Drug discovery, drug resistance, and pharmacological features of the above NRTIs and NNRTIs have been reviewed by previous studies\(^1^-^6,^8,^18^-^24\).

From 2010 to October 2021, the FDA approved three RT inhibitors: rilpivirine (RPV, Edurant\(^©\), approval date: 2011-05-20), tenofovir alafenamide (TAF, Vemlidy\(^©\), approval date: 2016-11-23), and cabotegravir (CAB, PrEP: Delstrigo\(^TM\), approval date: 2016-11-15).

![Figure 1](https://example.com/fig1.png) Approved antiretroviral regimens in the past decade (2010 to present). Most combination regimens are composed of two HIV nucleoside/nucleotide reverse transcriptase inhibitors plus one integrase inhibitor, one non-nucleoside reverse transcriptase inhibitor, or one protease inhibitor. Dapivirine vaginal ring 25 mg was approved by the European Medicines Agency on 24 July 2020, while the other regimens have been (tentatively) approved by the FDA.
10), and doravirine (DOR, Pifeltro™, approval date: 2018-08-30). These RT inhibitors are further integrated into 10 fixed-dose combination regimens that have been (tentatively) approved by the FDA (Table 1). In addition to these FDA-approved drugs, elsilfavirine (Elpida®/C226) was approved by the Russian Ministry of Health in June 2017. A vaginal ring containing dapivirine 25 mg was approved by the European Medicines Agency in July 2020. On 21 July 2021, azvudine was conditionally approved by the National Medical Products Administration in China.

To the best of our knowledge, no review has comprehensively characterized the drug discovery, clinical efficacy, and pharmacological profiles of newly-approved HIV RT inhibitors in the past decade. Based on a large body of randomized clinical trials, this review will summarize the clinical efficacy and pharmacological profiles of approved HIV RT inhibitors (tenofovir alafenamide, dapivirine, rilpivirine, doravirine, azvudine, elsilfavirine) and their combination regimens (Descovy®, Biktarvy®, Genvoya® Acriptega®, Symtuza®, Complera®, Juluca®, Cabenuva®, Delstrigo™).

This review is organized as follows. First, our strategies for literature search and selection are described. Second, for each approved RT inhibitor, we will highlight the (i) drug discovery; (ii) antiviral activity, drug resistance, and pharmacokinetics; and (iii) clinical efficacy and safety of their approved combination regimens in randomized clinical trials. Third, novel regimens will be highlighted. Our drug movies and teaching slides that highlight HIV RT inhibitors are shared online (www.virusface.com).

2. Search strategy and selection criteria

To collect relevant literature, we searched PubMed, Google Scholar, and Journal websites using the keywords of individual

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Figure 2  Structural basis of NRTI (islatravir) and NNRTI (doravirine). (A) Chemical and 3D structures of islatravir. The drug binding pocket of islatravir is highlighted in HIV-1 reverse transcriptase (PDB code: 5J2M). Islatravir triphosphate interferes with the translocation of HIV reverse transcription on the nucleic acid substrate to slow down the viral DNA synthesis. (B) Chemical and 3D structures of doravirine. Drug binding pocket of doravirine is highlighted at the palm domain of the P66 subunit in HIV-1 reverse transcriptase (PDB code: 4NCG). PDB codes were obtained from the RCSB protein data bank (www.rcsb.org/). Protein 3D structures were visualized by PyMOL V1.7 (www.pymol.org/).
drug names. We extracted clinical trial data from ClinicalTrials.gov (https://clinicaltrials.gov), drug labeling resources from the FDA database (www.accessdata.fda.gov), and drug resistance mutations from the IAS-USA guidelines. To summarize the clinical efficacy of approved combination regimens, we collected clinical studies that fulfilled four conditions: (i) randomized, controlled clinical trials must be at the stage of phases 2, 3, and/or 4; (ii) studies recruited adults in the absence of pregnant women; (iii) recruited adults were confirmed with HIV infections without other infectious diseases (e.g., tuberculosis, HBV, HCV) or non-communicable diseases such as liver/kidney impairment; (iv) patients were treated with the exact dosage of approved regimens according to the drug labeling; and (v) viral suppression of plasma HIV-1 RNA <50 copies/mL was measured at Week 48.

3. Tenofovir alafenamide (Vemlidy®)

In 2015, the FDA approved Genvoya®—the first combination regimen that contains tenofovir alafenamide (GS-7340) for the treatment of HIV-1 infections. Since then, five TAF-based combination regimens (Genvoya®, Odefsey®, Biktarvy®, Symtuza®, Descovy®) have been approved by the FDA and the European Medicines Agency (Table 1). The tentative approval of dolutegravir, emtricitabine, and tenofovir alafenamide tablets was granted by the FDA in December 2020, and this regimen is currently marked with the trade name of Acriptega® in India.

3.1. Drug discovery

As shown in Fig. 3A, the discovery of tenofovir alafenamide began with the synthesis of an adenosine nucleoside analogue called tenofovir [(R)-9-(2-phosphonylmethoxypropyl)adenine] at the Rega Institute in Belgium. Tenofovir showed potent activities against the replications of HIV-1 (EC50: 5.9 ± 0.45 µmol/L), HIV-2 (EC50: 4.9 ± 0.45 µmol/L), and HBV (EC50: 6.5 ± 1.1 µmol/L) in cell cultures. However, tenofovir carries negative charges on the phosphate moiety, resulting in poor cellular permeability and limited oral bioavailability. Many prodrugs of tenofovir such as TDF were subsequently developed to enhance the permeability across the intestinal wall. For instance, phosphoramidate prodrugs of tenofovir could be designed by the “ProTide” strategy that offers the efficient intracellular delivery of monophosphates and monophosphonates of nucleoside analogues across the cell membrane by passive diffusion.

A series of aryl phenoxy-amidate derivatives of tenofovir was synthesized and one potent candidate, designated as GS-7171, showed promising anti-HIV activity in vitro and oral bioavailability in dogs. Further purification of GS-7171 unexpectedly led to a 1:1 diastereomeric mixture of GS-7339 and GS-7340 due to the asymmetric center at the phosphorus atom of GS-7171 and the non-stereoselective synthetic process. Each stereoisomer was isolated using batch elution chromatography, and in vitro evaluations suggested that the anti-HIV-1 activity and pharmacokinetic profiles of GS-7340 were better than that of GS-7339. In fasted dogs, a single oral dose of TAF 10 mg-eq/kg preferentially produced a high concentration of tenofovir in lymphatic tissues and the peripheral blood mononuclear cells (PBMCs)—the primary location for HIV replication and latency. The intracellular concentrations of tenofovir, tenofovir-monophosphate, tenofovir-diphosphate, and TAF were respectively 138 ± 55, 89 ± 8, 73 ± 15, and 0 µmol/L in monocytes that were isolated from human whole blood after the incubation with TAF 17.4 µmol/L for 1 h. Based on the above findings, GS-7340 was selected as a potent anti-HIV inhibitor for further evaluations in clinical trials.

As the prodrugs of tenofovir, both TAF and TDF efficiently delivers tenofovir into lymphoid cells and tissues, and their structural differences can be traced to the phosphonate masking groups of TAF that harbor the phenol and alanine isopropyl ester (Fig. 3B). Compared with TDF, TAF is not only more stable in blood and plasma, but also maintains antiviral potency for a longer time and leads to higher levels of triglycerides, low-density and high-density lipoprotein cholesterol. Because the prolonged exposure to TDF 300 mg may increase the risk of renal

| Antiretroviral drug or regimen | Usage | Trade name | Region | First approval |
|-------------------------------|-------|------------|--------|----------------|
| Tenofovir alafenamide (TAF) 25 mg | With other drugs | Vemlidy® | US, EU | 2016-11-10 |
| TAF 25 mg + Emtricitabine (FTC) 200 mg | Pre-exposure prophylaxis | Descovy® | US, EU | 2019-10-03 |
| TAF 25 mg + FTC 200 mg + DRV 800 mg + COBI 150 mg | Complete regimen | Symtuza® | US, EU | 2018-07-17 |
| Rilpivirine (RPV) 25 mg | With other drugs | Edurant® | US, EU | 2011-05-20 |
| RPV 5 mg + FTC 200 mg + COBI 150 mg | Complete regimen | Complera® | US, EU | 2011-08-10 |
| RPV 5 mg + FTC 200 mg + BIC 50 mg | Complete regimen | Juluca® | US, EU | 2017-11-21 |
| RPV 300 mg/mL + CAB 200 mg/mL | Complete regimen | Cabenuva® | US, EU | 2021-01-21 |
| Doravirine (DOR) 100 mg | With other drugs | Pifeltro™ | US, EU | 2018-08-30 |
| DOR 100 mg + TDF 300 mg + FTC 300 mg | Complete regimen | Delstrigo™ | US, EU | 2018-08-30 |
| Elsulfavirine 20 mg | With other drugs | Elpida® | Russia | 2017-06-30 |
| Dapivirine 25 mg vaginal ring | Pre-exposure prophylaxis | — | EU | 2020-07-24 |
| Azvudine 3 mg | With other drugs | Azvudine Tablet | China | 2021-07-21 |

*A The TAF + FTC + DTG regimen is marked as the trade name of Acriptega® in India. The FDA granted the tentative approval of dolutegravir, emtricitabine, and tenofovir alafenamide tablets on 2020-12-04.

*B Descovy® was approved by the FDA for HIV-1 treatment and pre-exposure prophylaxis in 2016 and 2019, respectively.

*C Azvudine was conditionally approved in India.
impairment and a loss of bone mineral density\(^{17}\), TAF 25 mg offers lower systemic tenofovir exposure at reduced doses, thereby reducing renal and bone impairments\(^{17,42}\). TAF 10 or 25 mg/day is currently considered to replace TDF 300 mg/day in fixed-dose combinations.

3.2. Antiviral activity, drug resistance, and pharmacokinetics

TAF exhibited a strong potency against broad-spectrum isolates from HIV-1 groups/subtypes (EC\(_{50}\) range: 0.1–12 mmol/L) and HIV-2 (EC\(_{50}\) range: 0.91–2.63 mmol/L)\(^43\). In MT-2 cells infected with HIV-1 IIIb strain, the EC\(_{50}\) value of TAF (0.005 ± 0.002 mmol/L) was lower than that of TDF (0.05 ± 0.03 mmol/L) and tenofovir (5.0 ± 2.6 mmol/L)\(^38\). Despite its potency against HIV and HBV strains, TAF does not inhibit HCV, HSV-1, HCMV, dengue, or influenza A virus\(^39\). According to the recent update of IAS-USA guideline, TAF and TDF share similar drug-resistance profiles that include four primary amino acid substitutions: K65 R/E/N and K70E\(^25\).

In a phase 1b study of treatment-naive adults who received the monotherapy for 10 days, TAF 25 mg was quickly absorbed with the median T\(_{\text{max}}\) of 0.5 h\(^43\). At the steady-state, the plasma exposure of tenofovir on Day 10 was much lower in the treatment of TAF 25 mg (AUC\(_{\text{tau}}\): 267.7 ng-h/mL) compared with TDF 300 mg (1918.0 ng-h/mL)\(^43\). At approximately one-tenth of TDF 300 mg, TAF 25 mg offered a higher concentration of tenofovir-diphosphate in intracellular peripheral blood mononuclear cells (AUC\(_{\text{max}}\): 21.4 vs 3.0 mmol/L-h) (Fig. 3B). Due to its high oral bioavailability and solubility, TAF generates sufficient mass flux across the intestine to saturate efflux transport and reduce intestinal metabolisms\(^44\). In HIV-negative patients receiving TAF 25 mg, the pharmacokinetic parameters of C\(_{\text{max}}\) and AUC\(_{\text{tau}}\) were two times higher in patients with severe renal impairment than those with normal renal function (C\(_{\text{max}}\): 364 vs 199 ng/mL, AUC\(_{\text{tau}}\): 513 vs 267 ng-h/mL)\(^54\). The plasma exposure of its active metabolite tenofovir was significantly increased in individuals with severe renal impairment versus those with normal renal function (C\(_{\text{max}}\): 26.4 vs 9.5 ng/mL, AUC\(_{\text{tau}}\): 2070 vs 343 ng-h/mL)\(^55\).

The plasma concentration of TAF and its metabolites can be altered by the coadministration of other drugs that affect P-glycoprotein and/or breast cancer resistance protein transporters\(^46\). Pharmacokinetic boosters such as ritonavir and cobicistat inhibit the intestinal P-glycoprotein transporter to improve the intestinal absorption of TAF from the gastrointestinal tract\(^37\). In the presence of cobicistat, TAF could be reduced from 25 to 10 mg due to the boosting effects\(^48\). In the absence of any booster, TAF and TDF offered similar clinical efficacies and safety profiles in virologically suppressed adults with HIV-1\(^48\), and both exert an equivalent impact on the immune activation and inflammation in treatment-naive adults\(^39\).

3.3. Efficacy and safety of TAF-based combination regimens

3.3.1. TAF 25 mg + emtricitabine 200 mg (Descovy®)

In October 2019, the once-daily, fixed-dose, single-tablet of TAF 25 mg plus FTC 200 mg was approved by the FDA for at-risk HIV-negative adults (body weight ≥35 kg) to reduce the risk of HIV-1 infection from sexual acquisitions. The efficacy and safety of TAF + FTC in HIV-negative or transgender men who have sex with men (MSM) were evaluated by a phase three study called DISCOVER\(^30\). This randomized, double-blind, non-inferiority study reported the comparable incidence rates of HIV-1 infection between the TAF + FTC arm and the TDF + FTC arm (0.16 versus 0.34 infections per 100 person-years, P-value > 0.05), but the TAF-based regimen offered better safety on the bone mineral density and renal function\(^50\). Of note, the efficacy and safety of TDF + FTC versus the placebo group were previously confirmed\(^33\) (Table 2).

Due to the success of TDF + FTC in the pre-exposure prophylaxis of HIV-1 infections, TAF was considered for the replacement of TDF to develop the TAF + FTC regimen. Similar to TDF + FTC, TAF + FTC cannot be used in HIV-1-infected adults with the estimated creatinine clearance <30 mL/min. Ongoing clinical trials (e.g., NCT04616963, NCT04742491) will evaluate the efficacy and safety of TAF + FTC to prevent HIV-1 transmission in transgender-identifying or gender non-binary individuals.

3.3.2. TAF 25 mg + emtricitabine 200 mg + rilpivirine 25 mg (Odefsey®)

In March 2016, the FDA approved the three-drug, once-daily, fixed-dose tablet of TAF + FTC + RPV as the initiating therapy for treatment-naive patients or maintaining therapy for virologically suppressed patients. According to the drug labeling, TAF + FTC + RPV alone is not recommended for HIV-1-infected adults with HBV or creatinine clearance <30 mL/min.

The clinical efficacy and safety of TAF + FTC + RPV were evaluated by two phase 3b, non-inferiority studies (NCT02345226, NCT02345252) (Table 3, Supporting Information Table S1). Based on the merged data from the two studies above, TAF + FTC + RPV maintained the virological suppression (HIV-1 RNA <50 copies/mL at Week 48) in virologically suppressed adults infected with HIV-1. The drug-associated adverse events (e.g., upper respiratory tract infection, nasopharyngitis, headache, and diarrhea) were observed in 10.1% (76/754) of patients who received TAF + FTC + RPV.

3.3.3. TAF 25 mg + emtricitabine 200 mg + bictegravir 50 mg (Biktarvy®)

In February 2018, the FDA approved the three-drug fixed-dose regimen of TAF + FTC + BIC as initiating therapy for treatment-naive patients or maintaining therapy for virologically suppressed patients. According to the drug labeling, TAF + FTC + BIC alone is not recommended for the treatment of HIV-1-infected adults with HBV, severe hepatic impairment, or creatinine clearance <30 mL/min.

The clinical efficacy and safety of TAF + FTC + BIC were evaluated by one phase two study and seven phase three studies (Table 3). For treatment-naive adults, 91.4% (639/699) achieved the virological suppression after the 48-week treatment of TAF + FTC + BIC, and drug-associated adverse events were reported in 21.9% (139/634) participants. The 48-week treatment of TAF + FTC + BIC maintained HIV-1 RNA <50 copies/mL in 93.6% (1020/1090) patients of treatment-experienced adults who had been virologically suppressed for at least 3 months, while drug-associated adverse events were reported in 12.7% (138/1090) participants. In HIV-1-treatment-naive patients, the pre-existing resistance substitutions did not affect the virological outcomes of TAF + FTC + BIC, and no treatment-emergent resistance was observed after the 144-week treatment of TAF + FTC + BIC\(^52\). Ongoing clinical trials will evaluate the efficacy and safety of Biktarvy® in adolescents (NCT02881320), elderly patients...
3.3.4. TAF 25 mg + emtricitabine 200 mg + dolutegravir 50 mg

The tentative approval of TAF + FTC + DTG was granted by the FDA in December 2020, and its fixed-dose, single-tablet is now commercialized with the brand name of Acriptega in India. Although it has not been marketed in the USA, TAF + FTC + DTG is currently recommended by the IAS-USA and the EACS guidelines\textsuperscript{10,11}. Of note, TAF + FTC + DTG alone is not recommended for HIV-1-infected patients with body weight <40 kg, HBV infections, or creatinine clearance <30 mL/min.

The efficacy and safety of TAF + FTC + DTG were reported by four clinical studies (Table 3). In treatment-naïve patients who received TAF + FTC + DTG, 88.3% (626/709) achieved the virological response of HIV-1 RNA <50 copies/mL at Week 48. In virologically suppressed patients who received TAF + FTC + DTG, 91% (256/281) maintained the virological response of HIV-1 RNA <50 copies/mL at Week 48. The drug-associated adverse events were reported in 10% (28/281) patients (Table S1).

Figure 3  Discovery and metabolic pathway of tenofovir alafenamide. (A) Discovery of tenofovir alafenamide. Anti-HIV-1 parameters and pharmacokinetic values are extracted from\textsuperscript{38}. (B) Metabolic pathways of TDF 300 mg and TAF 25 mg from the gut to the blood plasma and lymphoid cells infected with HIV. At the steady-state, the plasma exposure of tenofovir at Day 10 was lower in the treatment of TAF 25 mg (AUC\textsubscript{tau} 267.7 ng·h/mL) compared with TDF 300 mg (1918.0 ng·h/mL)\textsuperscript{43}. TAF in blood enters primary hepatocytes and undertakes hydrolysis primarily by carboxylesterase one and cathepsin A that produce tenofovir-alanine conjugates within lymphocytes. TDF and TAF are converted to tenofovir and then phosphorylated to the intracellular active metabolite tenofovir diphosphate that blocks the catalytic site of HIV reverse transcriptase.
### Table 2 Efficacy of approved therapies for HIV-1 pre-exposure prophylaxis.

| Clinical trial (phase) | Recruited individuals | Trial arm | HIV infection no/patient no. | Person-years* | Incidence rate† | P-value | Ref. |
|-----------------------|-----------------------|-----------|-----------------------------|---------------|----------------|---------|------|
| DISCOVER (phase 3)    | HIV-negative or transgender MSM | TAF + FTC | 7/2694 | 8756 | 0.16% | >0.05 | 50 |
|                      |                      | TDF + FTC | 15/2693 | 3324 | 0.34% | NA | 51 |
|                      |                      | TDF + FTC | 38/1251 | NA | NA | NA | 51 |
| iPrEx (phase 3)       | HIV-negative or transgender MSM | Placebo | 72/1248 | NA | NA | NA | 51 |
| MTN-020—ASPIRE (phase 3) | HIV-negative women (18–45 years) | Dapivirine vaginal ring | 71/1313 | 4280 | 3.3% | 0.046 | 77 |
|                      |                      | Placebo | 97/1316 | 4.5% | NA | NA | 51 |
| Ring (phase 3)        | HIV-negative women (18–45 years) | Dapivirine vaginal ring | 77/1307 | 1888 | 4.1% | 0.04 | 78 |
|                      |                      | Placebo | 56/652 | 6.1% | NA | NA | 51 |

MSM: men who have sex with men.

*The person-years of follow-up are summarized for individual studies.

†Incidence rate equals the number of HIV-1 infections divided by person-years of follow-up. P-value indicates the statistical difference of incidence rates between the intervention arm and the placebo arm.

3.3.5. **TAF 10 mg + emtricitabine 200 mg + cobicistat 150 mg (Genvoya®)**

In November 2015, the FDA approved the once-daily, fixed-dose, single-tablet of TAF + FTC + EVG/c as initiating therapy and maintaining therapy to treat HIV-1-infected patients with no history of resistance to TAF, FTC, or EVG. According to the drug labeling, TAF + FTC + EVG/c alone is not recommended for HIV-1-infected patients with HBV infections, severe hepatic impairment, or creatinine clearance <30 mL/min. The clinical efficacy and safety of TAF + FTC + EVG/c were evaluated by one phase two study and four phase three studies (Table 3). The virological response of HIV-1 RNA <50 copies/mL at Week 48 was observed in 91.9% (899/978) of treatment-naive patients who received TAF + FTC + EVG/c (Table 3). By merging data from three phase three studies, this regimen offered the virological response up to 96.5% (1184/1227) of virologically suppressed patients (Table 3). Drug-associated adverse events were observed in 19.9% (244/1228) of patients receiving TAF + FTC + EVG/c.

A switch from TDF-based regimens to Genvoya® improved the bone mineral density in virologically suppressed patients ≥60 years (Table 3). Genvoya® also improved the bone mineral density in HIV-infected adults with renal impairment or with end-stage renal diseases on chronic hemodialysis. In a retrospective study of 6704 treatment-naive patients, HIV-1 RT amino acid substitutions such as T215 A/C/D/E/G/H/I/L/N/P/Q/R/S/V substitutions, including K65 R/N (2 cases, 0.2%) and M184V/I (11 cases, 1.3%) was observed in 866 treatment-naive adults who received TAF + FTC + EVG/c for 144 weeks.

3.3.6. **TAF 10 mg + emtricitabine 200 mg + darunavir 800 mg + cobicistat 150 mg (Symtuza®)**

In July 2018, the FDA approved the once-daily fixed-dose regimen of TAF + FTC + DRV/c as initiating therapy and maintaining therapy to treat HIV-1-infected patients with no history of resistance to TAF, FTC, or DRV. According to the drug labeling, TAF + FTC + DRV/c alone is not recommended for HIV-1-infected patients with body weight <40 kg. HBV infections, severe hepatic impairment, or creatinine clearance <30 mL/min.

The clinical efficacy and safety of TAF + FTC + DRV/c were evaluated by one phase two study and two phase three studies: AMBER and EMERALD (Table 3, Table S1). After the 48-week treatment with TAF + FTC + DRV/c, the virological response of HIV-1 RNA <50 copies/mL was observed in 88.2% (410/465) of treatment-naive adults and 95% (724/763) of virologically suppressed adults with virological suppression ≥6 months (Table 3). The most common drug-associated adverse event was upper respiratory tract infection (10.6%, 81/763) and nasopharyngitis (10.6%, 81/763) (Table S1).

4. Dapivirine

Dapivirine is a potent NNRTI against HIV-1 infections. On 24 July 2020, the European Medicines Agency approved dapivirine vaginal ring (a silicone elastomer dapivirine vaginal ring containing dapivirine 25 mg) for the pre-exposure prophylaxis of HIV-1 infection. The monthly application of dapivirine vaginal ring can be administered to reduce the risk of HIV-1 infection through vaginal intercourse in sexually active HIV-negative women (≥18 years) in combination with safer sex practices when oral pre-exposure prophylaxis is not/cannot be used or is not available.

4.1. **Drug discovery**

As shown in Fig. 4, the discovery of dapivirine can be traced back to the development of the alpha-anilinophenylacetamide (α-APA) derivatives, the imidoyl thiourea (ITU) derivatives, the diaryltriazine (DATA) derivatives, and the diarylpyrimidine (DAPY) derivatives based on the multidisciplinary collaborations between our Rega Institute in Belgium, Janssen Pharmaceutica in Belgium, and Rutgers University in the USA. In 1991, Pauwels et al. from our Rega Institute used a high-flux screening system to screen the Janssen library of 2000 different compounds for their cytotoxicity and capacity to inhibit HIV-1 replication in MT-4 cells. This led to the discovery of an alpha-anilinophenylacetamide lead called R1534557. Further optimization led to R89439 (loviride, loveride) that effectively inhibited HIV-1 strains in vitro at the nanomolar concentration (IC₅₀: 13 nmol/L). However, R89439 was later discontinued because it failed to show sufficient potency in clinical trials. Stemming from alpha-anilinophenylacetamide derivatives, imidoyl thiourea analogues with a unique diarylated imidoylthiourea structure was subsequently synthesized. However, these candidates were not further pursued due to the hydrolytic instability of the imidoyl thiourea functionality. During the synthesis of the imino-N-cyanoguanidine derivatives of imidoyl thiourea analogues,
a ring closure was unexpectedly identified, leading to the first compound of the DATA derivatives with improved stability. However, the DATA derivatives such as R106168 showed suboptimal activities against HIV-1 strains with the double mutant. However, the DATA derivatives such as R106168 showed suboptimal activities against HIV-1 strains with the double mutant.

b\[\text{EC}_{50}: 1 \text{ nmol/L}, \text{IC}_{50}: 24 \text{ nmol/L}\] in CEM T cells with a pyrimidine ring was evaluated, leading to the class of diarylpyrimidine derivatives such as dapivirine (TMC120, R147681) and etravirine (TMC125, R165335, Intercel®, approved by the FDA in 2008).

A vaginal microbiode of dapivirine was later considered because dapivirine has long half-life time, high potency, and low cytotoxicity. Although the applications of vaginally administered gel, film, tablet, soft gel capsules, and ring were considered to deliver dapivirine, the vaginal ring was eventually selected due to its easy use and a low frequency of the monthly administration. To prevent the male-to-female transmission of HIV-1 infections, the silicone elastomer intravaginal ring could provide the sustained and controlled delivery of dapivirine into cervicovaginal fluids and vaginal tissues. Other drug delivery methods such as gel products, fast-dissolving insert, lubricants and douches are still under investigation.

### 4.2. Antiviral activity, drug resistance, and pharmacokinetics

Dapivirine effectively prevented the HIV-1-induced syncytium formation with a 24-h treatment of dapivirine to the MO–DC/CD4+ T-cell cocultures also prevented the HIV-1 proviral integration with the required EC_{50}: 1 nmol/L, IC_{50}: 24 nmol/L in CEM T cells infected with HIV-1 strain HTHY-III. A 24-h treatment of dapivirine to the MO–DC/CD4+ T-cell cocultures also prevented the HIV-1 proviral integration.

| Table 3 | Clinical efficacy of approved anti-HIV regimens in phase 2/3 clinical trials. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Brand name**  | **Prior treatment** | **Arm** | **Efficacy** | **P-value** | **Study (phase)** | **Ref.** |
| Biktarvy®       | Treatment-naïve | TAF + FTC + BIC | 97% (63/65) | 0.17 | NCT02397694 | 178 |
|                 | Treatment-naïve | TAF + FTC + DTG | 91% (30/33) | 0.12 | NCT02607956 | 179 |
|                 | Treatment-naïve | TAF + FTC + BIC | 89% (286/320) | 0.12 | NCT02607956 | 179 |
|                 | Treatment-naïve | TAF + FTC + BIC | 93% (30/33) | 0.12 | NCT02607956 | 179 |
|                 | Treatment-naïve | ABC + 3TC + DTG | 92% (290/314) | 0.78 | NCT02607930 | 180 |
|                 | Virologically suppressed | ABC + 3TC + DTG | 93% (293/315) | 0.78 | NCT02607930 | 180 |
|                 | Virologically suppressed | ABC + 3TC + DTG | 94% (264/282) | 0.59 | NCT02603120 | 181 |
|                 | Virologically suppressed | ABC + 3TC + DTG | 95% (267/281) | 0.59 | NCT02603120 | 181 |
|                 | Virologically suppressed | TAF + FTC + BIC | 92% (267/290) | 0.20 | NCT02603107 | 182 |
|                 | Virologically suppressed | TAF + FTC + BIC | 96% (224/234) | 1.00 | NCT02652624 | 183 |
|                 | Virologically suppressed | TAF + FTC + BIC | 93% (265/284) | 0.28 | NCT03110380 | 184 |
|                 | Odefsey®          | TAF + FTC + DTG | 91% (256/281) | 0.28 | NCT03110380 | 184 |
|                 | Virologically suppressed | TAF + FTC + DTG | 90% (394/438) | 0.35 | NCT02345226 | 185 |
|                 | Virologically suppressed | TAF + FTC + DTG | 94% (296/316) | 1.00 | NCT02345252 | 186 |
|                 | Virologically suppressed | TAF + FTC + DTG | 94% (292/313) | 1.00 | NCT02345252 | 186 |
|                 | Acriptega®        | TAF + FTC + DTG | 84% (294/351) | 0.07 | NCT03122262 | 187 |
|                 | Treatment-naïve   | TDF + FTC + DTG | 85% (298/351) | 0.07 | NCT03122262 | 187 |
|                 | Virologically suppressed | TDF + FTC + DTG | 79% (276/351) | 0.07 | NCT03122262 | 187 |
|                 | Syntuza®          | TDF + FTC + DTG | 77% (79/103) | 0.41 | NCT01565850 | 188 |
|                 | Treatment-naïve   | TDF + FTC + DTG | 84% (42/50) | 0.41 | NCT01565850 | 188 |
|                 | Treatment-naïve   | TDF + FTC + DTG | 91% (331/362) | <0.0001 | NCT02431247 | 189 |
|                 | Treatment-naïve   | TDF + FTC + DTG | 88% (321/363) | 0.0001 | NCT02431247 | 189 |
|                 | Virologically suppressed | TDF + FTC + DTG | 95% (724/763) | 0.39 | NCT02269917 | 190 |
|                 | Virologically suppressed | TDF + FTC + DTG | 94% (354/378) | 0.39 | NCT02269917 | 190 |
|                 | Genvoya®          | TDF + FTC + DTG | 88% (99/112) | 0.84 | NCT01497899 | 191 |
|                 | Treatment-naïve   | TDF + FTC + DTG | 88% (51/58) | 0.84 | NCT01497899 | 191 |
|                 | Virologically suppressed | TDF + FTC + DTG | 92% (808/866) | 0.17 | NCT01780506 | 190 |
|                 | Virologically suppressed | TDF + FTC + DTG | 90% (784/867) | 0.17 | NCT01780506 | 190 |
|                 | Virologically suppressed | TDF + FTC + DTG | 97% (392/595) | 0.0002 | NCT01815376 | 192 |
|                 | Virologically suppressed | TDF + FTC + DTG | 93% (444/477) | 0.0002 | NCT01815376 | 192 |
|                 | Virologically suppressed | TDF + FTC + DTG | 94% (150/159) | 0.13 | NCT01705574 | 193 |
|                 | Virologically suppressed | TDF + FTC + DTG | 87% (46/53) | 0.13 | NCT01705574 | 193 |
|                 | Virologically suppressed | TDF + FTC + DTG | 94% (102/109) | 1.0 | NCT02616783 | 194 |
|                 | Virologically suppressed | TDF + FTC + DTG | 95% (52/55) | 1.0 | NCT02616783 | 194 |

aClinical efficacy was defined by HIV-1 RNA <50 copies/mL at Week 48.
K103N and/or Y191C73. However, L100I and/or K103N mutations may cause significant resistance to dapivirine74. Under suboptimal concentrations in vitro, drug resistance mutations were less frequent in the dapivirine + tenofovir group than in the dapivirine alone75. A significant decrease of fasting lipids (e.g., cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol) was observed in doravirine-treated patients76.

4.3. Efficacy and safety of dapivirine vaginal ring

Based on large-scale phase three studies77,78, the monthly application of dapivirine vaginal ring was evaluated for the pre-exposure prophylaxis of HIV-1 transmission in sexually active HIV-negative women (Table 2). The ASPIRE study, which was conducted between August 2012 and June 2015, reported the reduced incidence of HIV-1 infections at month 33 in the dapivirine-ring arm compared with the placebo arm (3.3 versus 4.5 seroconversions per 100 person-years, \( P = 0.046 \))77. Adverse events were 14% (180/1313) in the dapivirine-ring arm77. A follow-up study called HOPE was conducted between 16 July 2016 and 10 October 2018, and this study reported the reduced HIV-1 incidences of 2.7 per 100 person-years in the dapivirine-ring arm compared with the expected incidence of 4.4 per 100 person-years from the ASPIRE study79. Moreover, the dapivirine ring made of the flexible silicone matrix polymers unlikely caused cervical cytology abnormalities80. In the ring study, the overall incidence rate of HIV-1 infections in the dapivirine arm was significantly lower than that in the placebo arm (4.1 versus 6.1 seroconversions per 100 person-years, \( P = 0.04 \))81. Three NNRTI resistance mutations were identified, including E138A (11.7%, 9/77), A98G (3.9%, 3/77), and K103N (3.9%, 3/77)80. As an open-label extension of the Ring study, the DREAM study supported the clinical use of the dapivirine ring with low HIV-1 incidences and improved adherence81. Ongoing open-label studies will evaluate the dapivirine-containing vaginal ring in young women between 16 and 21 years (NCT03593655), pregnant women (NCT03965923), and women who are breastfeeding (NCT04140266).

5. Rilpivirine (Edurant®, Rekambys®)

Rilpivirine (other names: TMC278, R278474) is a diarylpyrimidine NNRTI approved by the FDA in 2011. Rilpivirine tablets...
5.1. Drug discovery

Rilpivirine is the E-isomer of the p-cyanovinyl analogue of dapivirine. As shown in Fig. 5, the discovery of rilpivirine began with the prototype of the diarylpyrimidine dapivirine82. Molecular modeling analyses suggested that the para substitutions on the trisubstituted phenyl ring of compound 5 may improve the drug interactions with the conserved W229 region in the drug-binding pocket of HIV-1 RT, therefore benefiting its antiviral activity against HIV-1 mutants82. This hypothesis led to the introduction of a spacer group G between the trisubstituted phenyl ring and the cyano group in the 4-position of compound 6 (Fig. 5). A series of substitutions at the G position was subsequently evaluated, leading to the discovery of rilpivirine with the promising potency against single- and double-mutant HIV-1 strains in vitro82.

5.2. Antiviral activity, drug resistance, and pharmacokinetics

Rilpivirine exhibits broad-spectrum antiviral activities against viral strains from HIV-1 genotypes (A1, C, D, F1, G, H) and CRFs (AE, AG, BG) with the EC50 values ranging from 0.13 to 0.44 nmol/L83,84. Based on in vitro experiments, rilpivirine actively inhibits HIV-1 group O isolates (EC50: 2.88–8.45 nmol/L)85. According to the IAS-USA guideline, resistance mutations to rilpivirine include L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, with the EC50 values ranging from 0.13 to 0.44 nmol/L83,84. Importantly, common NNRTI-associated resistance mutations (e.g., V106 and G190) do not decrease the sensitivity to rilpivirine86.

In a phase 2a study of treatment-naive patients (n = 9) who received rilpivirine 25 mg for 7 days, the pharmacokinetic parameters of rilpivirine included mean Cmax: 263 ng/mL, Tmax: 4 h, t1/2: 34–55 h, and AUC24 h: 3659 ± 885 ng h/mL83. Rilpivirine is largely insoluble in water and oils, supporting its development as a nanosuspension86. In HIV-infected patients who received the monthly injection of rilpivirine plus cabotegravir, the total drug concentration was 134 (83–187) ng/mL of rilpivirine and 3.02 (2.37–5.10) μg/mL of cabotegravir in plasma that were collected 7 (±3) days post-injection87.

5.3. Efficacy and safety of rilpivirine-based combination regimens

5.3.1. Rilpivirine 25 mg + TDF 300 mg + emtricitabine 200 mg (Complera®)

In August 2011, the FDA approved the regimen of RPV + TDF + FTC as the initial therapy for treatment-naive patients and the maintaining therapy for virologically-suppressed patients. According to the drug labeling, TDF + FTC + RPV alone is not recommended for HIV-1-infected adults with HBV, bodyweight <35 kg, or creatinine clearance <50 mL/min. The efficacy and safety of TDF + FTC + RPV were evaluated by at least three phase three studies (Table 4). When TDF + FTC + RPV was used as the initial therapy, 84.5% (625/740) of treatment-naive patients achieved HIV-1 RNA <50 copies/mL at Week 48. When this regimen was applied as the maintaining therapy, 93.9% (294/313) of virologically-suppressed patients maintained HIV-1 RNA <50 copies/mL at Week 48. The drug-associated adverse events were reported in 11.8% (37/314) of patients who received TDF + FTC + RPV.

5.3.2. Rilpivirine 25 mg + dolutegravir 50 mg (Juluca®)

In November 2017, the two-drug complete regimen of RPV + DTG was approved as the maintaining therapy to treat virologically suppressed patients who had no history of treatment failure and no drug resistance profiles associated with RPV or DTG. The efficacy and safety of RPV + DTG were reported by one phase three study89. The virological suppression of HIV-1 RNA <50 copies/mL at Week 48 was identified in 94.7% (486/513) of virologically suppressed patients (Table 4). The drug-associated adverse events were reported in 19% (97/513) of patients who received RPV + DTG.

5.3.3. Rilpivirine 300 mg/mL + cabotegravir 200 mg/mL (Cabenuva®)

In January 2021, the FDA approved the monthly intramuscular injection of rilpivirine (RPV) plus cabotegravir (CAB) extended-release injectable suspension for virologically-suppressed patients with no history of treatment failure and with no known resistance to RPV or CAB. According to the drug labeling, the tolerability of RPV and CAB should be assessed before the initiating therapy of RPV + CAB. Due to drug–drug interactions, the coadministration of RPV + CAB plus other drugs with a known risk of Torsade de Pointes should be cautious.

The efficacy and safety of the RPV + CAB injection was evaluated by one phase two study called LATTE-2 and three phase three clinical trials called FLAIR, ATLAS, and ATLA-2M (Table 4). By merging the data from the four studies above, the virological response of HIV-1 RNA <50 copies/mL at Week 48 was maintained in 93.1% (1144/1229) of virologically-suppressed patients who received the monthly intramuscular injection of RPV + CAB. The drug-associated adverse events were reported in 28.3% (167/591) of patients who received RPV + CAB. The 96-week findings from the FLAIR study reaffirmed the durability of RPV + CAB in virologically-suppressed adults89. Ongoing clinical trials will evaluate the oral and long-acting injectable regimen of rilpivirine plus cabotegravir in virologically suppressed children and adolescents (NCT03497676), patients across European countries (NCT04399551), and patients treated with the RPV + CAB injection every 2 months (NCT03299049).

6. Doravirine (DOR, Pifeltro™)

Doravirine, also named MK-1439, is an FDA-approved NNRTI with the brand name Pifeltro™ (Table 1). According to the drug labeling, the oral use of doravirine 100 mg should be combined with other antiretroviral drugs for the treatment of HIV-1 infections in treatment-naive adults.
6.1. Drug discovery

As shown in Fig. 6, the discovery of doravirine began with the high-throughput screening that identified the lead tetrazole thioacetanilide inhibitor (compound 7) of HIV-1 RT using a cell-based assay. Subsequent optimizations were conducted by the substitution of the labile 2-nitroanilide with the more stable anilide structure (compound 8), thereby improving the oral bioavailability and decreasing the plasma clearance. However, these tetrazole thioacetanilide analogues showed suboptimal pharmacokinetic profiles ($t_{1/2}/C_{20}=1.1$ h) in animal models. Inspired by the structural comparisons of compounds 8 and 9, a series of diaryl ether analogues such as compound 10 was synthesized because the diaryl ether may improve the drug binding to inhibit HIV-1 mutant strains with better pharmacokinetic results.

Further analysis of structure–activity relationship led to the optimization of a diaryl ether/indazole compound 11 that inhibited HIV-1 wildtype and mutant strains with L100I, K103N, Y181C and/or G190A/S (IC50 range: 2.6–171 nmol/L). Due to the low solubility and poor oral bioavailability of compound 11 ($F$: 3.3% in rats), a pyridine ring was considered to modify the phenyl ring of the indazole moiety in compound 11, leading to the development of compound 12 with better pharmacokinetic profiles ($F$: 52%). Next, the aryl ether core of compound 12 was replaced by a pyridone ring to increase the polarity and the binding affinity, thereby identifying the pyridone compound 13 with better antiviral activity against HIV-1 strains with the K103N + Y181C mutation. To improve the plasma half-life, the replacement of chloride in compound 13 ($t_{1/2}$: 2 h) with the strong electron withdrawing CF3 group led to compound 14, resulting in a longer elimination half-life ($t_{1/2}$: 7 h in rats). The alkylated pyridone in compound 14 was modified to disrupt the strong donor–acceptor hydrogen bonds to improve aqueous solubility, eventually leading to the discovery of doravirine with potent pharmacokinetic and antiviral activities against HIV-1 strains with the K103N + Y181C mutation.

6.2. Antiviral activity, drug resistance, and pharmacokinetics

Drug resistance to doravirine is mostly associated with three primary RT mutations (V106 A/M, Y188L) and 11 secondary RT mutations (V106T/I, Y188 C/H, G190E, P225H, F227 C/L/R, M230L, L234I) in vitro assays supported the antiviral potency of doravirine against a broad range of different HIV-1 subtype strains and mutant viruses with K101E, K103N, E138K, Y181C, M184V/I, and/or G190A. Doravirine-associated resistance mutations were very rare (1.4%; 137/9764) according to a large-scale cohort of 9764 treatment-naive patients from Greece, Italy, and France. A significant increase of doravirine-associated resistance mutations (V106 A/M, V108I, Y188 L/C/H, G190E, F227L, M230L, K103N + P225H) was observed in a large cohort of 6893 patients treated with other NNRTIs (delavirdine, efavirenz, nevirapine, etravirine, rilpivirine). Doravirine 100 mg/day can be orally taken with or without food and its clinical potency is unlikely altered by host factors (e.g., gender, age, race), severe renal impairment, and modest hepatic impairment. In six healthy males, the pharmacokinetic profiles of single-dose doravirine 100 mg were estimated, including mean $C_{\text{max}}$: 171.17 nmol/L, $C_{24}$: 95.43 nmol/L, AUCinf: 38.32 μmol/L-h, and AUC24: 22.84 μmol/L-h. In 12 healthy males who received the intravenous injection of a single-dose doravirine 100 μg, doravirine metabolites were mostly distributed in feces (84.1% of the dose recovered up to 168 h) and urine (2.2% of the dose recovered up to 96 h).
According to the drug labeling, doravirine should not be co-administered with strong CYP3A4 inducers (e.g., efavirenz, rifampin) that significantly decrease the plasma concentration of doravirine, resulting in the reduced virological response and possible drug resistance. However, doravirine is unlikely involved with other CYP enzymes (e.g., CYP3A5, CYP1A2, CYP2B6, CYP2C8) and drug transporters (e.g., organic anion transporting polypeptide 1B1)\textsuperscript{106,107}. Moreover, doravirine unlikely interacts with other drugs such as TDF, lamivudine, atorvastatin, methadone, elbasvir, grazoprevir, ledipasvir, and sofosbuvir\textsuperscript{108,109}. 6.3. Efficacy and safety of doravirine-based combination regimens

6.3.1. Doravirine 100 mg + TDF 300 mg + lamivudine 300 mg (Delstrigo\textsuperscript{TM})

In August 2018, the FDA approved the once-daily fixed-dose regimen of TDF + 3TC + DOR for treatment-naive adults infected with HIV-1 infections. According to the drug labeling, TDF + 3TC + DOR alone is not recommended for HIV-1-infected adults with HBV or creatinine clearance <50 mL/min. The clinical efficacy and safety of TDF + 3TC + DOR were evaluated by one phase two study \textsuperscript{10} and three phase three studies: DRIVE-AHEAD, DRIVE-FORWARD, and DRIVE-SHIFT (Table 4 and Table S1). In treatment-naive patients who received TDF + 3TC + DOR for 48 weeks, the clinical efficacy of HIV-1 RNA <50 copies/mL at Week 48 was 83.5% (278/333) in the DRIVE-FORWARD study, 84.3% (307/364) in the DRIVE-AHEAD study, and 100% (8/8) in the single-arm, open-label, phase two study \textsuperscript{12}. Drug-associated adverse events were observed in 31% (113/364) of patients receiving TDF + 3TC + DOR. The most common adverse events include dizziness, abnormal dreams, and nausea. In the DRIVE-SHIFT study of treatment-experienced patients with the virological suppression for ≥6 months, treatment switching from the baseline regimen to TDF+3TC+DOR maintained the virological suppression of HIV-1 RNA <50 copies/mL at Week 48 in 90.8% (406/447) patients (Table 4). Ongoing clinical trials will report the potential application of doravirine 100 mg plus TAF 25 mg and FTC 200 mg to maintain the viral suppression in treatment-experienced adults (NCT04079452, NCT04097925).

6.3.2. Doravirine 100 mg + islatravir 0.75 mg + lamivudine 300 mg (novel regimen)

Doravirine was evaluated with the once-daily combination of lamivudine and islatravir for the treatment of previously untreated adults with HIV-1 infections based on a phase 2b, randomized, double-blind study \textsuperscript{116}. At Week 48, the virological suppression of HIV-1 RNA <50 copies/mL was observed in 90% (27/30) of participants receiving the regimen of doravirine 100 mg + islatravir 0.75 mg + lamivudine 300 mg \textsuperscript{116}. The clinical efficacy was 84% (26/31) in the control group of doravirine 100 mg + TDF 300 mg + lamivudine 300 mg \textsuperscript{117}. The ongoing phase three studies will evaluate doravirine 100 mg plus islatravir 0.75 mg in treatment-naive adults (NCT04233879), virologically suppressed adults (NCT04223778, NCT04223791), pediatric patients (NCT04295772), and heavily treatment-experienced adults (NCT04233216).

7. Azvudine (FNC)

On 2021 July 21, azvudine was conditionally approved by the National Medical Products Administration in China. As shown in Fig. 7, the discovery of azvudine (2’-deoxy-2’-β-fluoro-4’-azidocytidine) began with the initial search of antiviral inhibitors that target HCV RNA-dependent RNA polymerase \textsuperscript{118}. In 2001, 2’-C-methylcytidine (compound 15, NM107) was discovered as a potent nucleoside inhibitor of Flaviviridae virus in cell cultures, but its further development was hampered by its low oral bioavailability \textsuperscript{119}. Subsequent design of 4’-substituted cytidine analogues led to the synthesis of 4’-azidocytidine.

### Table 4 Clinical efficacy of approved anti-HIV regimens in phase 2/3 clinical trials.

| Brand name       | Prior treatment | Arm                     | Efficacy \(^a\) | P-value | Study (phase) | Ref.       |
|------------------|----------------|-------------------------|-----------------|---------|--------------|------------|
| **Complera\textsuperscript{®}** |                |                         |                 |         |              |            |
| Treatment-naive  |                | RPV + TDF + FTC         | 83% (287/346)   | 0.17    | NCT00540449  | 195        |
| Treatment-naive  |                | EFV + TDF + FTC         | 83% (285/344)   |         | NCT01309243  | 196        |

| Juluca\textsuperscript{®} | Virologically suppressed | RPV + DTG            | 95% (486/513)  | 0.90    | NCT02429791  | 88         |

| Cabenuva\textsuperscript{®} | Virologically suppressed | RPV + CAB (monthly)  | 91% (105/115) | 0.82    | NCT02120352  | 197        |

| Delstrigo\textsuperscript{TM} | Virologically suppressed | RPV + CAB (monthly)  | 94% (265/283) | 0.87    | NCT02938520  | 198        |

| **Delstrigo\textsuperscript{TM}** | Treatment-naive     | DOR + TDF + 3TC       | 83% (278/333) | 0.34    | NCT02775780  | 202        |

| Virologically suppressed | DOR + TDF + 3TC     | 89% (307/364)          | 0.24           |         |              |            |

| Virologically suppressed | DOR + TDF + 3TC     | 84% (294/358)          | 0.24           |         |              |            |

| Virologically suppressed | DOR + TDF + 3TC     | 84% (306/383)          | 0.24           |         |              |            |

| **Delstrigo\textsuperscript{TM}** | Virologically suppressed | DOR + TDF + 3TC     | 84% (43/50)    |         |              |            |

| Virologically suppressed | DOR + TDF + 3TC     | 80% (306/383)          | 0.24           |         |              |            |

| Virologically suppressed | DOR + TDF + 3TC     | 80% (306/383)          | 0.24           |         |              |            |

### Notes:

\( ^a \) Clinical efficacy was defined by HIV-1 RNA <50 copies/mL at Week 48.
(compound 16, R1479) to inhibit HCV chain elongation.\(^{112}\) With the inversion of the 2’-hydroxyl group, the 4’-azido-arabinocytidine (compound 17, RO-9187) showed better phosphorylation efficiency than compound 16.\(^{114}\) Because fluoronucleosides are often good substrates of RNA polymerases, the monofluoro and difluoro analogues of 4’-azidocytidine were subsequently designed, leading to the optimization of azvudine (RO-0622) and compound 18.\(^{113}\) In the HCV replicon system, azvudine (EC\(_{50}\): 24 nmol/L) showed better antiviral potency than compound 18 (EC\(_{50}\): 4020 nmol/L)\(^{113}\). Moreover, azvudine exhibited broad-spectrum antiviral activities against HIV,\(^{115}\) HBV,\(^{116}\) and SARS-CoV-2,\(^{117}\) but not respiratory syncytial virus or influenza A virus.\(^{118}\) In cell cultures, azvudine inhibited various strains from HIV-1 subtype B and recombinants B/C and CRF01_AE (EC\(_{50}\): 0.03–6.92 nmol/L).\(^{113}\) Regarding its mechanisms of action, azvudine may inhibit HIV-1 RT and target the Vif-containing E3 ubiquitin ligase complex to block the Vif-induced degradation of APOBEC3G.\(^{117}\) Moreover, azvudine is mainly metabolized by CYP3A, and its absolute oral bioavailability is 82.7% in dog plasmas.\(^{121}\)

A phase two study evaluated the safety and efficacy of azvudine (NCT04109183, completion date: 6 March 2019), but its clinical results have not been published as of today. An ongoing phase three trial will evaluate the efficacy and safety of azvudine 3 mg plus TDF 300 mg and EFV 200 mg in treatment-naive patients infected with HIV-1 (NCT04303598). Future studies also need to address the advantage of azvudine over FDA-approved NRTIs such as TAF.

8. Elsulfavirine (Elpida\(^{®}\))

Elsulfavirine, the prodrug of the active NNRTI VM1500A (Fig. 8A), was approved by the Russian Ministry of Health in 2017. Although the discovery of elsulfavirine has not been documented yet in peer-reviewed literature, pharmacokinetic
features of elsulfavirine 20 mg were characterized by a preclinical study\textsuperscript{127}. In four healthy individuals treated with a single-dose of elsulfavirine 20 mg, the VM-1500A metabolite was measured with a mean half-life $t_{1/2}$: 8.9 ± 2 days, $T_{\text{max}}$: 0.15 ± 0.04 days, $C_{\text{max}}$: 98 ± 74.3 ng/mL, and AUC$_{\text{inf}}$: 829 ± 507 ng·h/mL\textsuperscript{123}. In HIV-infected patients receiving elsulfavirine 20 mg for 7 days, the pharmacokinetic parameters of the VM-1500A metabolite included (i) $t_{1/2}$: 7.4 ± 1.6 days, (ii) $T_{\text{max}}$: 6.3 ± 0.5 days, (iii) $C_{\text{max}}$: 148 ± 8 ng/mL, and (iv) AUC$_{\text{inf}}$: 2123 ± 266 ng·h/mL\textsuperscript{122}. Elsulfavirine 20 mg is now considered with the once-daily combination of TDF 300 mg and emtricitabine 200 mg. A phase 2b study evaluated the efficacy and safety of elsulfavirine 20 mg versus efavirenz 600 mg in combination with TDF + FTC\textsuperscript{125}. In treatment-naive patients, the efficacy of HIV-1 plasma RNA <50 copies/mL at Week 48 was higher in the elsulfavirine arm (81%, 44/55) than in the efavirenz arm (74%, 35/47)\textsuperscript{123}. A follow-up study reported the virological suppression of HIV RNA <50 copies/mL at week 96 in 83.9% (73/87) of treatment-naive patients who continued the treatment of elsulfavirine 20 mg plus TDF + FTC\textsuperscript{124}. The drug-associated adverse events were reported in 23.3% (14/60)\textsuperscript{124}. Ongoing trials will report the drug–drug interactions (NCT03709355) and the feasibility of the once-weekly administration of elsulfavirine (NCT03730311).

9. Development of novel NRTIs and NNRTIs

A large number of novel NRTIs and NNRTIs have been reported in the literature\textsuperscript{6,125–128, but only a few candidates are currently evaluated by clinical trials. Most candidates were discontinued because of their limited efficacy, unfavorable side effects, and/or high toxicity. For example, (i) lersivirine (UK-453061) was discontinued in 2013 because lersivirine showed no advantage over the existing NNRTIs; (ii) fosdevirine was halted in 2014 due to unexpected side effects such as seizures; (iii) censavudine was discontinued in 2015 due to the success of tenofovir alafenamide with better clinical efficacy and safety profiles\textsuperscript{129}; and (iv) apricitabine was discontinued in 2015 due to the success of censavudine. No advantage over the existing NNRTIs; (ii) fosdevirine was discontinued because of their limited efficacy, unfavorable side effects, and/or high toxicity. For example, (i) lersivirine (UK-453061) was discontinued in 2013 because lersivirine showed no advantage over the existing NNRTIs; (ii) fosdevirine was halted in 2014 due to unexpected side effects such as seizures; (iii) censavudine was discontinued in 2015 due to the success of tenofovir alafenamide with better clinical efficacy and safety profiles\textsuperscript{129}; and (iv) apricitabine was discontinued in 2015 due to the success of censavudine. No advantage over the existing NNRTIs; (ii) fosdevirine was halted in 2014 due to unexpected side effects such as seizures; (iii) censavudine was halted in 2015 due to the success of tenofovir alafenamide with better clinical efficacy and safety profiles\textsuperscript{129}; and (iv) apricitabine was halted in 2015 due to the success of censavudine.

9.1. Ilatravir (MK-8591, EFdA)

Ilatravir, known as MK-8591 or EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine), is a deoxyadenosine nucleoside analogue (Fig. 8B) that targets the reverse transcriptase of HIV-1, HIV-2, and SIV\textsuperscript{130–133}. Unlike the conventional chain-terminating NRTIs, ilatravir acts as an effective immediate or delayed chain terminator depending on the sequence of the nucleic acid substrate\textsuperscript{134}. The biocatalytic cascade synthesis of ilatravir could be efficiently made by five engineered enzymes with four auxiliary enzymes\textsuperscript{135}. Ilatravir offers potent antiviral activities (EC$_{50}$ ≤ 11 nmol/L) against broad-spectrum viral isolates with multi-drug resistant mutations (e.g., K65R, Q151M, M184V)\textsuperscript{135}. The EC$_{50}$ values of ilatravir were less than 21 nmol/L against a variety of HIV-1 strains (e.g., HIV-1$_{\text{NL4-3}},$ HIV-1$_{\text{MDR}},$ HIV-1$_{\text{Ba-L}}$)\textsuperscript{136}. In cell-based assays, an apparent synergism of ilatravir plus rilpivirine may enhance the antiviral and prophylactic activity against HIV-1\textsuperscript{137}. Pharmacokinetics features such as $C_{\text{max}}$: 3.2 nmol/mL, $T_{\text{max}}$: 0.5 h, and AUC$_{12\ h}$: 9.5 nmol/h·mL were measured after the oral administration of ilatravir in 25 humanized mice infected with HIV-1$_{\text{NL4-3}}$.

The once-weekly oral dosing of ilatravir (1.3 or 0.43 mg/kg/week for 6 weeks) protected all male rhesus macaques (n = 8) from intrarectal challenges with SIV and HIV\textsuperscript{139}. A single subcutaneous administration of ilatravir-eluting implants in rodents and rhesus macaques sustained the drug release at clinically relevant concentrations for at least 6 months\textsuperscript{140}. In a phase one study (NCT02217904), a single dose of ilatravir 0.5 mg suppressed HIV-1 RNA levels by more than one log on Day 7 in 30 treatment-naive adults\textsuperscript{141}. The prophylaxis activity of ilatravir is currently evaluated by phase three clinical studies of cisgender women (NCT04644029) and men and transgender women who have sex with men (NCT04652700).

9.2. MK-8504 and MK-8583

Similar to TAF, MK-8504 and MK-8583 are prodrugs of tenofovir that can be intracellularly converted to the active form of tenofovir-diphosphate\textsuperscript{142}. Two phase one studies evaluated the single-dose pharmacokinetics, antiviral activities, and safety of MK-8504 (NCT03188523) and MK-8583 (NCT03552536). In HIV-negative patients, MK-8504 and MK-8583 were rapidly absorbed ($T_{\text{max}}$: 0.5 h) and eliminated from plasma\textsuperscript{142}. Both compounds were well-tolerated with only mild to moderate adverse events\textsuperscript{132}. The efficacy and safety of MK-8503 and MK-8583 in once-weekly regimens are yet to be clarified.

9.3. MK-8507

As a novel NNRTI with two trifluoromethyl groups, MK-8507 could be a potential once-weekly oral regimen against HIV-1 infection\textsuperscript{143}. In healthy adults without HIV infection, a long terminal half-life of MK-8507 ($t_{1/2}$ range: 58–84 h) was observed across different doses and MK-8507 was unlikely a strong inducer of CYP3A4\textsuperscript{144}. In treatment-naïve patients infected with HIV-1, the single-dose monotherapy of MK-8507 (80 mg) reduced the plasma HIV-1 RNA by $1.5$ ($1.8$ to $1.19$) log$_{10}$ copies/mL at 7-day post-dose and its plasma pharmacokinetics were measured as follows: terminal $t_{1/2}$: 69.4 h, $T_{\text{max}}$: 2.0 h, $C_{\text{max}}$: 2.11 μmol/L and AUC$_{0-\text{inf}}$: 129 μmol·h/L\textsuperscript{145}. In vitro IC$_{50}$ of MK-8507 was 5.3 nmol/L based on the Monogram’s PhenoSense assay\textsuperscript{145}. Moreover, MK-8507 maintained the in vitro potency against NNRTI-resistant-associated variants such as K103N, Y181C and G190A\textsuperscript{145}. A phase 2 study (NCT04564547) was planned to evaluate the once-weekly two-drug regimen of MK-8507 (100, 200, 400 mg) plus ilatravir 20 mg for the treatment of HIV-1 infection. On 18 November 2021, however, the development of MK-8507 was temporarily paused by Merck due to side effects (e.g., decreases in total lymphocyte and CD4+ T-cell counts) in the phase 2 study.

9.4. IQP-0528

IQP-0528 (SJ-3991) is a novel NNRTI that inhibits the viral reverse transcription and the viral entry of HIV-1 and HIV-2\textsuperscript{146}. A dual chamber vaginal/rectal microbicide gel called DuoGelTM inhibited the CCR5-tropic subtype B strain HIV-1$_{\text{US/92/727}}$ with the EC$_{50}$ values of 4.11–4.79 nmol/L\textsuperscript{147}. IQP-0528 gel is a
promising candidate to protect human polarized ectocervical tissues against HIV-1 infections, because of its dual mechanisms of action and its minimal toxicity to vaginal cells and natural flora. In a phase one study, seven HIV-negative individuals received one 10 mL rectal dose of 1% IQP-0528 gel, and no drug-associated adverse event was observed (NCT03082690). However, the application of IQP-0528 is limited because of its rapid clearance and its inability to penetrate vaginal tissues following the rectal dosing.

9.5. MIV-150

MIV-150 (Fig. 8B) is a novel NNRTI with antiviral activities against HIV-1 replications. Although the oral use of MIV-150 was discontinued because of its poor systemic absorption and rapid systemic clearance, a novel core-matrix intravaginal ring called PC-1005 was proposed in the combination of (i) MIV-150 plus zinc acetate to prevent HSV-2 infections; (ii) MIV-150 plus carrageenan to prevent the infections of HSV-2 and human...
papillomavirus; and (iii) MIV-150 plus levonorgestrel to prevent the HIV-1, HSV-2, human papillomavirus, and unintended pregnancy. In a phase one study (NCT02033109), the vaginal use of PC-1005 was well-tolerated with low systemic levels in sexually abstinent, HIV-negative women. Another phase one study will evaluate PC-1005 as a rectal microbicide in HIV-negative adults with a history of consensual anal intercourse (NCT03408899).

10. Conclusions

In this study, we provide a comprehensive review of approved RT inhibitors and their combination regimens in the past decade. Although the development of each approved RT inhibitor had a different story, their drug discovery all requires coordinated multidisciplinary efforts from medicinal chemists, virologists, pharmacists, crystallographers, and many others. Tenofovir alafenamide was discovered as the phenyl monoester isopropyl alaninyl phosphoramidate of tenofovir based on an unexpected observation of the mixture GS-7171, while its clinical approval was only granted 15 years later after its discovery. Although rilpivirine and dapivirine were both originated from the α-APA derivatives, rilpivirine was developed as once-daily oral tablets and dapivirine was applied as the vaginal ring application due to their different oral bioavailability and half-life time. Elsulfavirine has been approved only in Russian, while its clinical advantage requires further investigations. Moreover, many drugs (e.g., doravirine) were developed with a series of structure-guided optimizations, thereby highlighting the importance of crystallography in antiviral drug discovery.
Our review summarized the clinical efficacy and safety of approved anti-HIV regimens based on randomized controlled trials. In clinical studies of HIV-1 pre-exposure prophylaxis, TAF + FTC and dapivirine vaginal ring significantly reduced the incidence rate of HIV infections (Table 2). To treat HIV-1 infections in treatment-naïve patients, the highest efficacy was observed in the initial therapy of TAF + FTC + EVG/c (91.9%, 899/978), followed by 3TC + DTG (91.5%, 655/716), TAF + FTC + BIC (91.4%, 639/699), ABC+3TC + DTG (90.1%, 657/729), TDF + FTC + EVG/c (94.5%, 1456/1626), TAF + FTC + DTG (88.3%, 626/709), TAF + FTC + DRV/c (88.2%, 410/465), TDF + FTC + RPV (84.5%, 625/740), and TDF+3TC + DOR (83.9%, 585/697) (Fig. 9A). Drug-associated adverse events of preceding regimens included diarrhea, headache, and nasopharyngitis (Fig. 9B). In the treatment of virologically suppressed patients with HIV-1 infections, the highest efficacy was observed in the maintaining therapy of TAF + FTC + EVG/c (96.5%, 1184/1227), followed by TAF + FTC + DRV/c (94.9%, 724/763), RPV + DTG (94.7%, 486/513), TDF + FTC + EVG/c (94.5%, 52/55), TDF + FTC + RPV (93.9%, 294/313), TAF + FTC + BIC (93.6%, 1020/1090), RPV + FTC + CAB (93.1%, 1144/1229), 3TC + DTG (93.0%, 384/413), TAF + FTC + RPV (91.5%, 690/754), TAF + FTC + DTG (91.1%, 256/281), TDF+3TC + DOR (90.8%, 406/447), and ABC+3TC + DTG (90.3%, 758/839) (Fig. 9A). The drug-associated adverse events of the preceding regimens include nasopharyngitis, diarrhea, and headache (Fig. 9B). Among these regimens, only two NRTI-free regimens (RPV + DTG, RPV + CAB) have been approved, but they are often used as maintaining therapies rather than initial therapies.

In clinical practice, once-daily fixed-dose regimens of two NRTIs (TAF + FTC, TDF + FTC, TDF+3TC) plus another drug (e.g., integrase inhibitors) have been widely applied as the standard of care for most patients infected with HIV-1 infections. Of note, TAF is now gradually replacing TDF as the backbone in the once-daily, fixed-dose, single-tablet regimens such as Odefsey®, Genvoya®, and Descovy® because TAF offers high potency and safety profiles in the life-long treatment of HIV infections. Three NRTIs (TAF, TDF, lamivudine) have usually replaced another drug has been approved for the treatment of age-related macular degeneration that causes blindness in humans. HIV RT inhibitors have been initially proposed to treat coronavirus disease 2019 (COVID-19), which has caused a global pandemic with severe morbidity and mortality since the end of 2019. As of today, no anti-HIV drug has been approved for the treatment of COVID-19, whereas TDF + FTC could reduce the risk of COVID-19 and hospitalization in HIV-positive patients.

Future development of antiretroviral regimens could be conceived as follows: (i) the development of novel inhibitors with better potency and safety profiles, and longer half-life for long-acting applications; (ii) new applications of approved inhibitors in two-drug regimens, long-acting formulations, and once-daily, fixed-dose, single-tablet regimens; and (iii) weekly or monthly applications of novel regimens in the HIV pre-exposure prophylaxis. Novel extended-release delivery devices such as vaginal rings, nanoformulations, and subcutaneous implants also provide new options to deliver antiretroviral drugs weekly, monthly, and maybe even yearly. In the foreseeable future, antiretroviral regimens will play a significant role in saving the lives of millions of human beings worldwide.

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Author contributions

Guangdi Li and Yali Wang performed the literature search and data collection. Erik De Clercq conceived the concept of the study. Guangdi Li, Yali Wang and Erik De Clercq prepared and revised the manuscript. All authors read and approved the final paper.
Conflicts of interest

Prof. Dr. Erik De Clercq was the co-inventor of tenofovir. We declare no competing interests.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2021.11.009.

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