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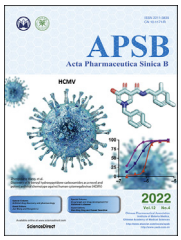

REVIEW

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 elsulfavirine) 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.

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; CC_{50}, the 50% cytotoxic concentration; COBI, cobicistat; DOR, doravirine; DPV, dapivirine; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EC_{50}, half maximal effective concentration; EFV, efavirenz; ESV, elsulfavirine; 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; IC_{50}, 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; $t_{1/2}$, 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)[1−7]. 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[1,4,5,8]. 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 (EVG) 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-

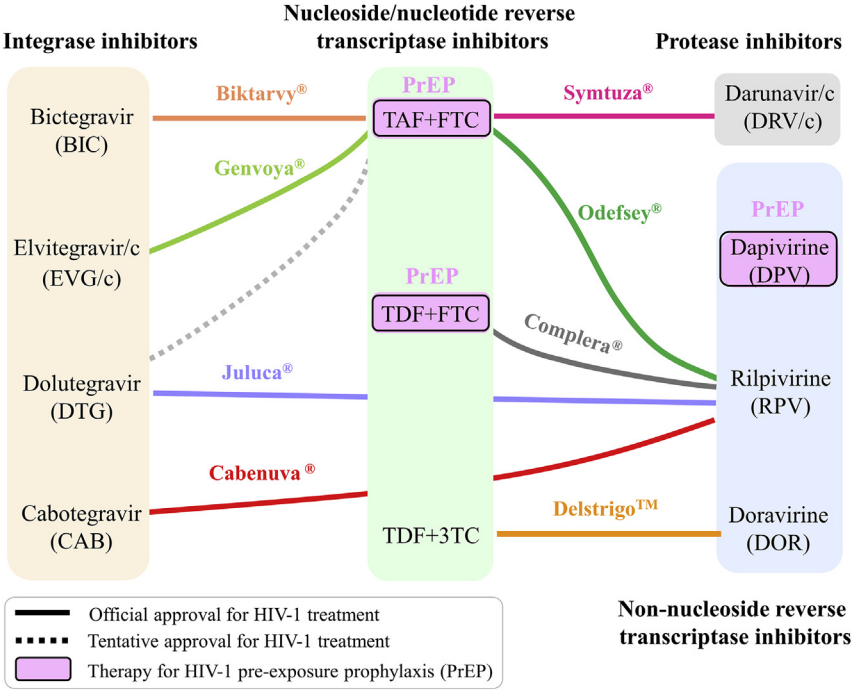

Figure 1 Approved antiretroviral regimens in the past decade (2010 to present). Most combination regimens are composed of two HIV nucleoside/nucleotide reverse transcriptase inhibitors plus one integrase inhibitor, one non-nucleoside reverse transcriptase inhibitor, or one protease inhibitor. Dapivirine 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.

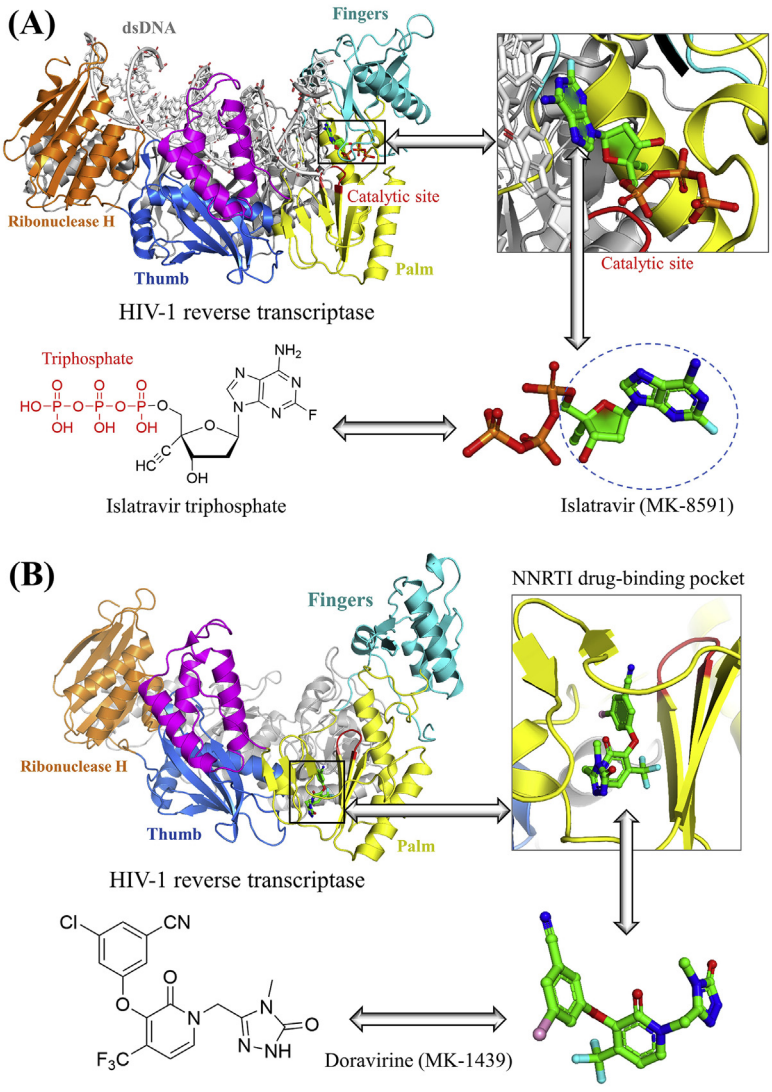

Figure 2 Structural basis of NRTI (islatravir) and NNRTI (doravirine). (A) Chemical and 3D structures of islatravir. The drug binding pocket of islatravir is highlighted in HIV-1 reverse transcriptase (PDB code: 5J2M). Islatravir triphosphate interferes with the translocation of HIV reverse transcription 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/).

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, elsulfavirine (Elpida®) 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, elsulfavirine) 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

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[25]. 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[26], HCV[27,28]) 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[29]. Tenofovir showed potent activities against the replications of HIV-1 (EC_{50}: 5.9 ± 0.45 μmol/L)[29], HIV-2 (EC_{50}: 4.9 ± 0.45 μmol/L)[29], and HBV (EC_{50}: 6.5 ± 1.1 μmol/L) in cell cultures[30]. However, tenofovir carries negative charges on the phosphonate moiety, resulting in poor cellular permeability and limited oral bioavailability[31,32]. Many prodrugs of tenofovir such as TDF were subsequently developed to enhance the permeability across the intestinal wall[33]. 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[34,35].

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[36]. 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[37]. Each stereoisomer was isolated using batch elution chromatography[37], and *in vitro* evaluations suggested that the anti-HIV-1 activity and pharmacokinetic profiles of GS-7340 were better than that of GS-7339[38]. 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[38]. 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[38]. 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[39] and leads to higher levels of triglycerides, low-density and high-density lipoprotein cholesterol[40]. Because the prolonged exposure to TDF 300 mg may increase the risk of renal

Table 1 List of approved HIV RT inhibitors and their regimens in the past decade.

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[b]
TAF 25 mg + FTC 200 mg + RPV 25 mg	Complete regimen	Odefsey®	US, EU	2016-03-01
TAF 25 mg + FTC 200 mg + BIC 50 mg	Complete regimen	Biktarvy®	US, EU	2018-02-07
TAF 25 mg + FTC 200 mg + DTG 50 mg	Complete regimen	Acriptega®[a]	US[a], India	2020-12-04[a]
TAF 10 mg + FTC 200 mg + EVG 150 mg + COBI 150 mg	Complete regimen	Genvoya®	US, EU	2015-11-05
TAF 10 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 25 mg + TDF 300 mg + FTC 200 mg	Complete regimen	Complera®	US, EU	2011-08-10
RPV 25 mg + DTG 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 + 3TC 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[c]	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 China.

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[41,42]. 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 nmol/L) and HIV-2 (EC_{50} range: 0.91−2.63 nmol/L)[39]. In MT-2 cells infected with HIV-1 IIIb strain, the EC_{50} value of TAF (0.005 ± 0.002 μmol/L) was lower than that of TDF (0.05 ± 0.03 μmol/L) and tenofovir (5.0 ± 2.6 μmol/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-naïve adults who received the monotherapy for 10 days, TAF 25 mg was quickly absorbed with the median T_{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_{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_{tau}: 21.4 *vs* 3.0 μmol/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_{max} and AUC_{inf} were two times higher in patients with severe renal impairment than those with normal renal function (C_{max}: 364 *vs* 199 ng/mL, AUC_{inf}: 513 *vs* 267 ng·h/mL)[45]. The plasma exposure of its active metabolite tenofovir was significantly increased in individuals with severe renal impairment *versus* those with normal renal function (C_{max}: 26.4 *vs* 9.5 ng/mL, AUC_{inf}: 2070 *vs* 343 ng·h/mL)[45].

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[47]. 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-naïve adults[49].

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[50]. 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[51] (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-naïve 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-naïve 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-naïve 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-naïve 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

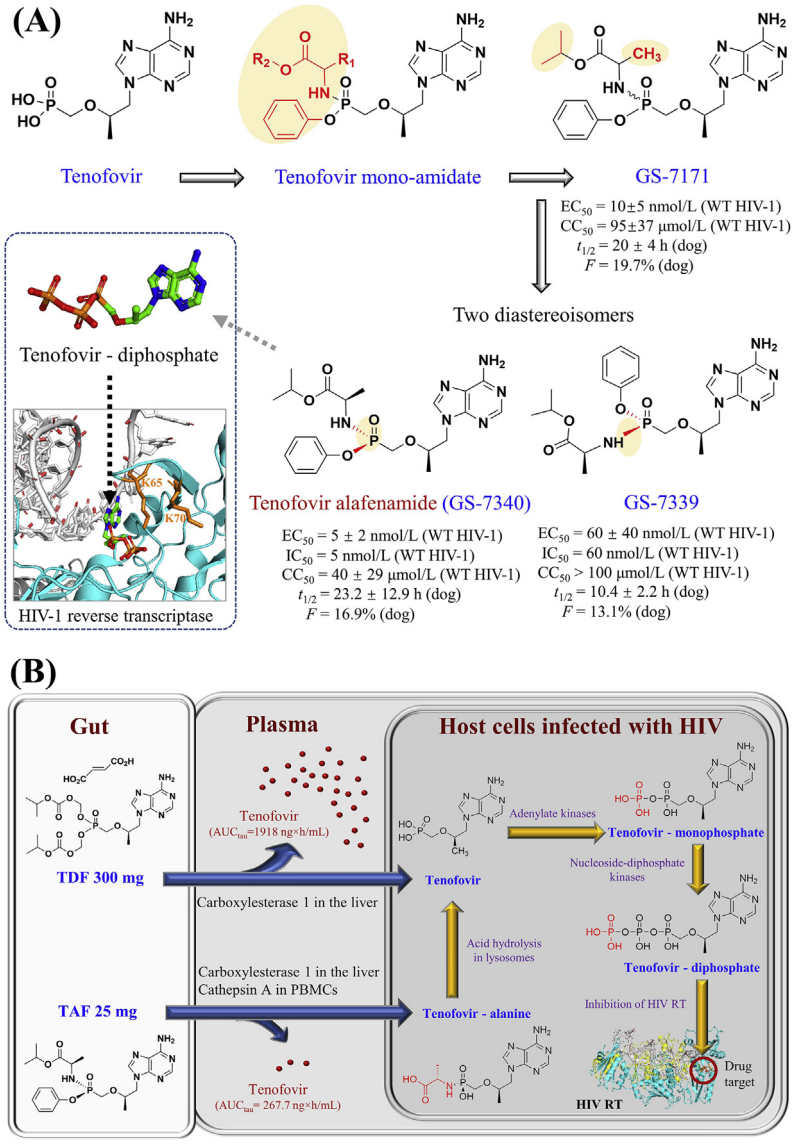

Figure 3 Discovery and metabolic pathway of tenofovir alafenamide. (A) Discovery of tenofovir alafenamide. Anti-HIV-1 parameters and pharmacokinetic values are extracted from[38]. (B) Metabolic pathways of TDF 300 mg and TAF 25 mg from the gut to the blood plasma and lymphoid cells infected with HIV. At the steady-state, the plasma exposure of tenofovir at Day 10 was lower in the treatment of TAF 25 mg (AUC_{tau}: 267.7 ng·h/mL) compared with TDF 300 mg (1918.0 ng·h/mL)[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.

(NCT04222283), HIV-positive renal transplant patients (NCT04530630), patients within 100 days post HIV infections (NCT04483674), and patients co-infected with tuberculosis (NCT04734652).

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[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).

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[a]	Incidence rate[b]	*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		0.34%		
iPrEx (phase 3)	HIV-negative or transgender MSM	TDF + FTC	38/1251	3324	NA	NA	51
		Placebo	72/1248		NA		
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%		
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%		

MSM: men who have sex with men.
[a]The person-years of follow-up are summarized for individual studies.
[b]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 + elvitegravir 150 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-naïve 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[53] or with end-stage renal diseases on chronic hemodialysis[54]. 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 showed no measurable impact on virological responses to TAF + FTC + EVG/c[55]. A low prevalence of resistant RT mutations, including K65 R/N (2 cases, 0.2%) and M184V/I (11 cases, 1.3%) was observed in 866 treatment-naïve adults who received TAF + FTC + EVG/c for 144 weeks[56].

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-naïve 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[57], the imidoyl thiourea (ITU) derivatives[58], the diarylt riazine (DATA) derivatives[59], and the diarylpyrimidine (DAPY) derivatives[60] based on the multidisciplinary collaborations between our Rega Institute in Belgium[61], Janssen Pharmaceutica in Belgium, and Rutgers University in the USA[62]. In 1991, Pauwels et al.[57] 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 R15345[57]. Further optimization led to R89439 (loviride, loveride) that effectively inhibited HIV-1 strains *in vitro* at the nanomolar concentration (IC_{50}: 13 nmol/L)[57]. 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[58]. However, these candidates were not further pursued due to the hydrolytic instability of the imidoyl thiourea functionality[58]. During the synthesis of the imino-*N*-cyanoguanidine derivatives of imidoyl thiourea analogues,

Table 3 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.
Biktarvy®	Treatment-naive	TAF + FTC + BIC	97% (63/65)	0.17	NCT02397694 (phase 2)	178
		TAF + FTC + DTG	91% (30/33)			
	Treatment-naive	TAF + FTC + BIC	89% (286/320)	0.12	NCT02607956 (phase 3)	179
		TAF + FTC + DTG	93% (302/325)			
	Treatment-naive	TAF + FTC + BIC	92% (290/314)	0.78	NCT02607930 (phase 3)	180
		ABC + 3TC + DTG	93% (293/315)			
	Virologically suppressed	TAF + FTC + BIC	94% (264/282)	0.59	NCT02603120 (phase 3)	181
		ABC + 3TC + DTG	95% (267/281)			
	Virologically suppressed	TAF + FTC + BIC	92% (267/290)	0.20	NCT02603107 (phase 3)	182
		PI-based regimen	89% (255/287)			
	Virologically suppressed	TAF + FTC + BIC	96% (224/234)	1.00	NCT02652624 (phase 3)	183
		Baseline regimen	95% (225/236)			
	Virologically suppressed	TAF + FTC + BIC	93% (265/284)	0.28	NCT03110380 (phase 3)	184
		TAF + FTC + DTG	91% (256/281)			
Odefsey®	Virologically suppressed	TAF + FTC + RPV	90% (394/438)	0.35	NCT02345226 (phase 3)	185
		TDF + FTC + EFV	92% (402/437)			
	Virologically suppressed	TAF + FTC + RPV	94% (296/316)	1.00	NCT02345252 (phase 3)	186
		TDF + FTC + RPV	94% (294/313)			
Acriptega®	Treatment-naive	TAF + FTC + DTG	84% (294/351)	0.07	NCT03122262 (phase 3)	187
		TDF + FTC + DTG	85% (298/351)			
		TDF + FTC + EFV	79% (276/351)			
Symtuza®	Treatment-naive	TAF + FTC + DRV/c	77% (79/103)	0.41	NCT01565850 (phase 2)	188
		TDF + FTC + DRV/c	84% (42/50)			
	Treatment-naïve	TAF + FTC + DRV/c	91% (331/362)	<0.0001	NCT02431247 (phase 3)	189
		TDF + FTC + DRV/c	88% (321/363)			
	Virologically suppressed	TAF + FTC + DRV/c	95% (724/763)	0.39	NCT02269917 (phase 3)	190
		TDF + FTC + PI	94% (354/378)			
Genvoya®	Treatment-naive	TAF + FTC + EVG/c	88% (99/112)	0.84	NCT01497899 (phase 2)	191
		TDF + FTC + EVG/c	88% (51/58)			
	Treatment-naive	TAF + FTC + EVG/c	92% (800/866)	0.17	NCT01780506 NCT01797445 (phase 3)	40
		TDF + FTC + EVG/c	90% (784/867)			
	Virologically suppressed	TAF + FTC + EVG/c	97% (932/959)	0.0002	NCT01815736 (phase 3)	192
		TDF-based regimen	93% (444/477)			
	Virologically suppressed	TAF + FTC + EVG/c	94% (150/159)	0.13	NCT01705574 (phase 3)	193
		TDF + FTC + ATV/r	87% (46/53)			
	Virologically suppressed	TAF + FTC + EVG/c	94% (102/109)	1.0	NCT02616783 (phase 3)	194
		TDF + FTC + EVG/c	95% (52/55)			

[a]Clinical efficacy was defined by HIV-1 RNA <50 copies/mL at Week 48.

a ring closure was unexpectedly identified[62], leading to the first compound of the DATA derivatives with improved stability[59]. However, the DATA derivatives such as R106168 showed suboptimal activities against HIV-1 strains with the double mutant L100I + K103N[59]. After the exploration of the structure–activity and structure−metabolism relationships, the replacement of the central aminotriazine ring of DATA with a pyrimidine ring was evaluated, leading to the class of diarylpyrimidine derivatives such as dapivirine (TMC120, R147681)[63] and etravirine (TMC125, R165335, Intelence®, approved by the FDA in 2008)[64].

A vaginal microbicide of dapivirine was later considered because dapivirine has long half-life time, high potency, and low cytotoxicity[65,66]. 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[67]. 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[68]. Other drug delivery methods such as gel products, fast-dissolving insert, lubricants and douches are still under investigation[69].

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

Dapivirine effectively prevented the HIV-1-induced syncytium formation (EC_{50}: 1 nmol/L, IC_{50}: 24 nmol/L) in CEM T cells infected with HIV-1 strain HTLV-III_B[63]. A 24-h treatment of dapivirine to the MO−DC/CD4+ T-cell cocultures also prevented the HIV-1 proviral integration (EC_{50}: 4 nmol/L, range: 0.5−15 nmol/L)[70]. Over a 28-day use of the vaginal ring containing dapivirine 25 mg, dapivirine distributed throughout the lower genital tract of HIV-negative women at a concentration of 4000 times higher than the required EC_{50} against wildtype HIV-1 strains in MT4 cells[71]. After the ring insertion for 1.5 h, the C_{max} value of dapivirine was the highest near the ring (79.90 ± 23.20 μg/g), followed by the cervix (66.61 ± 20.12 μg/g) and the introitus (31.38 ± 10.95 μg/g) in healthy women[72].

A high concentration of dapivirine in the genital tract maintained a strong inhibition against HIV-1 resistant viruses including those with

K103N and/or Y191C[73]. However, L100I and/or K103N mutations may cause significant resistance to dapivirine[74]. Under suboptimal concentrations *in vitro*, drug resistance mutations were less frequent in the dapivirine + tenofovir group than in the dapivirine alone[75]. A significant decrease of fasting lipids (*e.g.*, cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol) was observed in doravirine-treated patients[76].

4.3. *Efficacy and safety of dapivirine vaginal ring*

Based on two large-scale phase three studies[77,78], 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*-value = 0.046)[77]. Adverse events were 14% (180/1313) in the dapivirine-ring arm[77]. 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 study[79]. Moreover, the dapivirine ring made of the flexible silicone matrix polymers unlikely causeed cervical cytology abnormalities[80]. 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*-value = 0.04)[78]. Three NNRTI resistance mutations were identified, including E138A (11.7%, 9/77), A98G (3.9%, 3/77), and K103N (3.9%, 3/77)[78]. 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 adherence[81]. 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

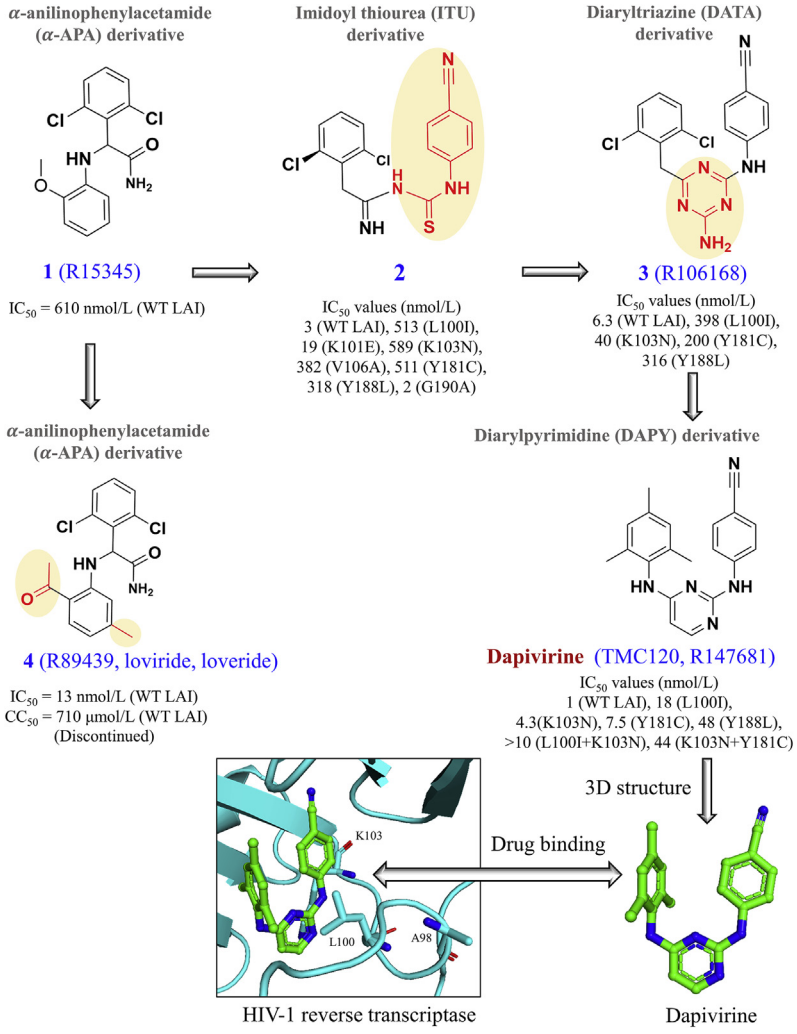

Figure 4 Discovery of dapivirine from the alpha-anilinophenylacetamide (α-APA) derivatives to imidoyl thiourea derivatives, the diaryltriazine derivatives, and the diarylpyrimidine derivatives. Drug binding pocket of dapivirine is highlighted in HIV-1 reverse transcriptase (PDB code: 1S6Q). Amino acid positions with drug resistant residues are highlighted. Three amino acid substitutions (L100I, K103N, A98G) may cause resistance to dapivirine[74,78].

(Edurant®) and injection (Rekambys®) are both marketed. According to the FDA labeling, the once-daily tablet of rilpivirine 25 mg in combination with other antiretroviral drugs can be orally taken with a meal to treat HIV-1 infections in treatment-naïve patients (>12 years) with bodyweight ≥35 kg, $CD4^+$ cell count >200 cells/mm^3, and HIV-1 RNA ≤100,000 copies/mL. According to the drug labeling, rilpivirine should not be coadministered with cytochrome P450 inducers (*e.g.*, rifabutin, rifampin, rifapentine) or drugs (*e.g.*, cimetidine, famotidine, nizatidine) that increase gastric pH, because these drugs may reduce the plasma concentration of rilpivirine and cause the reduced virologic response and possible drug resistance.

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 dapivirine[62]. 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 mutants[82]. 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 vitro*[82].

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 EC_{50} values ranging from 0.13 to 0.44 nmol/L[83,84]. Based on *in vitro* experiments, rilpivirine actively inhibits HIV-1 group O isolates (EC_{50}: 2.88−8.45 nmol/L)[83]. According to the IAS-USA guideline, resistance mutations to rilpivirine include L100I, K101 E/P, E138 A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, and M230I/L[25]. Importantly, common NNRTI-associated resistance mutations (*e.g.*, V106 and G190) do not decrease the sensitivity to rilpivirine[83].

In a phase 2a study of treatment-naïve patients ($n = 9$) who received rilpivirine 25 mg for 7 days, the pharmacokinetic parameters of rilpivirine included mean C_{max}: 263 ng/mL, T_{max}: 4 h, $t_{1/2}$: 34−55 h, and $AUC_{24\ h}$: 3659 ± 885 ng h/mL[85]. Rilpivirine is largely insoluble in water and oils, supporting its development as a nanosuspension[86]. In HIV-infected adults 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-injection[87].

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-naïve 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-naïve 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 study[88]. 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 adults[89]. 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-naïve adults.

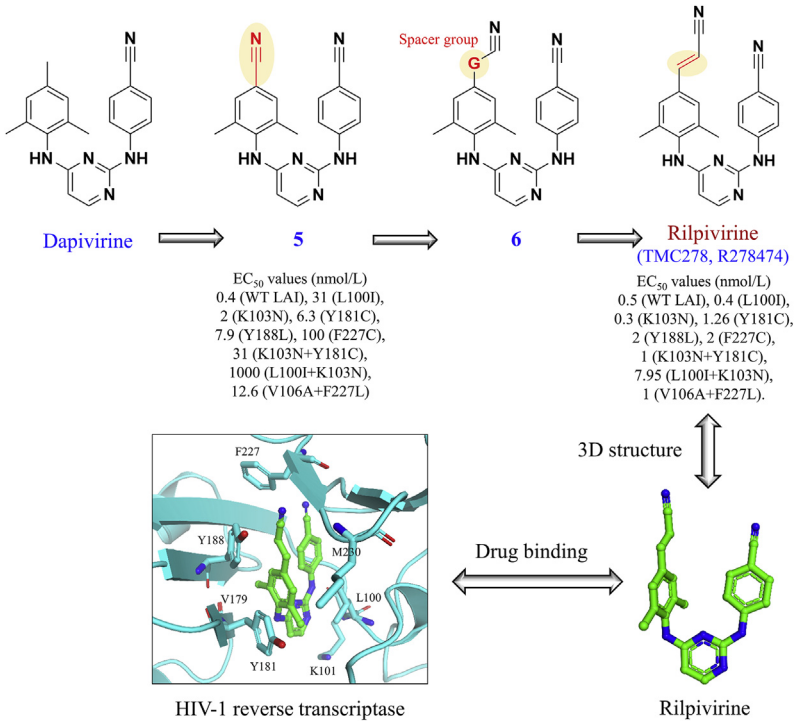

Figure 5 Discovery of rilpivirine based on the template of dapivirine. EC_{50} values are obtained from Ref. 82. Drug binding pocket of rilpivirine is highlighted in HIV-1 reverse transcriptase (PDB code: 3MEG). Amino acid positions with known resistant residues are highlighted.

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[90]. 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[90]. However, these tetrazole thioacetanilide analogues showed suboptimal pharmacokinetic profiles ($t_{1/2} \leq 1.1$ h) in animal models[91]. 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[91]. 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 G190 A/S (IC_{50} range: 2.6−171 nmol/L)[91].

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 (*e.g.*, *F*: 52%)[92]. 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[93]. To improve the plasma half-life, the replacement of chlorine in compound **13** ($t_{1/2}$: 2 h) with the strong electron withdrawing CF_3 group led to compound **14**, resulting in a longer elimination half-life ($t_{1/2}$: 7 h in rats)[94]. 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[94].

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)[25]. *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[95−98]. Doravirine-associated resistance mutations were very rare (1.4%; 137/9764) according to a large-scale cohort of 9764 treatment-naïve patients from Greece, Italy, and France[99]. 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)[100].

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)[101], severe renal impairment[102], and modest hepatic impairment[103]. In six healthy males, the pharmacokinetic profiles of single-dose doravirine 100 mg were estimated, including mean C_{max}: 1713.17 nmol/L, $C_{24\ h}$: 593.43 nmol/L, AUC_{inf}: 38.32 μmol/L·h, and $AUC_{24\ h}$: 22.84 μmol/L·h[104]. 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)[105].

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®	Treatment-naive	RPV + TDF + FTC	83% (287/346)	0.17	NCT00540449	195
		EFV + TDF + FTC	83% (285/344)		(phase 3)	
	Treatment-naive	RPV + TDF + FTC	86% (338/394)	0.12	NCT01309243	196
		EFV + TDF + FTC	82% (320/394)		(phase 3b)	
Juluca®	Virologically	RPV + DTG	95% (486/513)	0.90	NCT02429791	88
	suppressed	ART regimen	95% (485/511)		NCT02422797	
					(phase 3)	
Cabenuva®	Virologically	RPV + CAB (monthly)	91% (105/115)	0.82	NCT02120352	197
	suppressed	RPV + CAB (bimonthly)	92% (106/115)		(phase 2b)	
		ABC + 3TC + CAB	89% (50/56)			
	Virologically	RPV + CAB (monthly)	94% (265/283)	0.87	NCT02938520	198
	suppressed	ABC + 3TC + DTG	93% (264/283)		(phase 3)	
	Virologically	RPV + CAB (monthly)	93% (285/308)	0.13	NCT02951052	199
	suppressed	ART regimen	96% (294/308)		(phase 3)	
	Virologically	RPV + CAB (monthly)	93% (489/523)	0.61	NCT03299049	200
	suppressed	RPV + CAB (bimonthly)	94% (492/522)		(phase 3b)	
Delstrigo™	Treatment-naive	DOR + TDF + 3TC	84% (307/364)	0.24	NCT02403674	201
		EFV + TDF + FTC	81% (294/364)		(phase 3)	
	Treatment-naive	DOR + TDF + 3TC	83% (278/333)	0.34	NCT02275780	202
		DOR + ABC + 3TC	86% (43/50)		(phase 3)	
		PI-based regimen	80% (306/383)			
	Virologically	DOR + TDF + 3TC	91% (406/447)	0.12	NCT02397096	203
	suppressed	Baseline regimen	95% (211/223)		(phase 3)	

[a]Clinical efficacy was defined by HIV-1 RNA <50 copies/mL at Week 48.

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)[106,107]. Moreover, doravirine unlikely interacts with other drugs such as TDF, lamivudine, atorvastatin, methadone, elbasvir, grazoprevir, ledipasvir, and sofosbuvir[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™)*

In August 2018, the FDA approved the once-daily fixed-dose regimen of TDF + 3TC + DOR for treatment-naïve 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[110] and three phase three studies: DRIVE-AHEAD, DRIVE-FORWARD, and DRIVE-SHIFT (Table 4 and Table S1). In treatment-naïve 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[110]. 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[111]. 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[111]. The clinical efficacy was 84% (26/31) in the control group of doravirine 100 mg + TDF 300 mg + lamivudine 300 mg[111]. The ongoing phase three studies will evaluate doravirine 100 mg plus islatravir 0.75 mg in treatment-naïve 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[112]. 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[113]. Subsequent design of 4′-substituted cytidine analogues led to the synthesis of 4′-azidocytidine

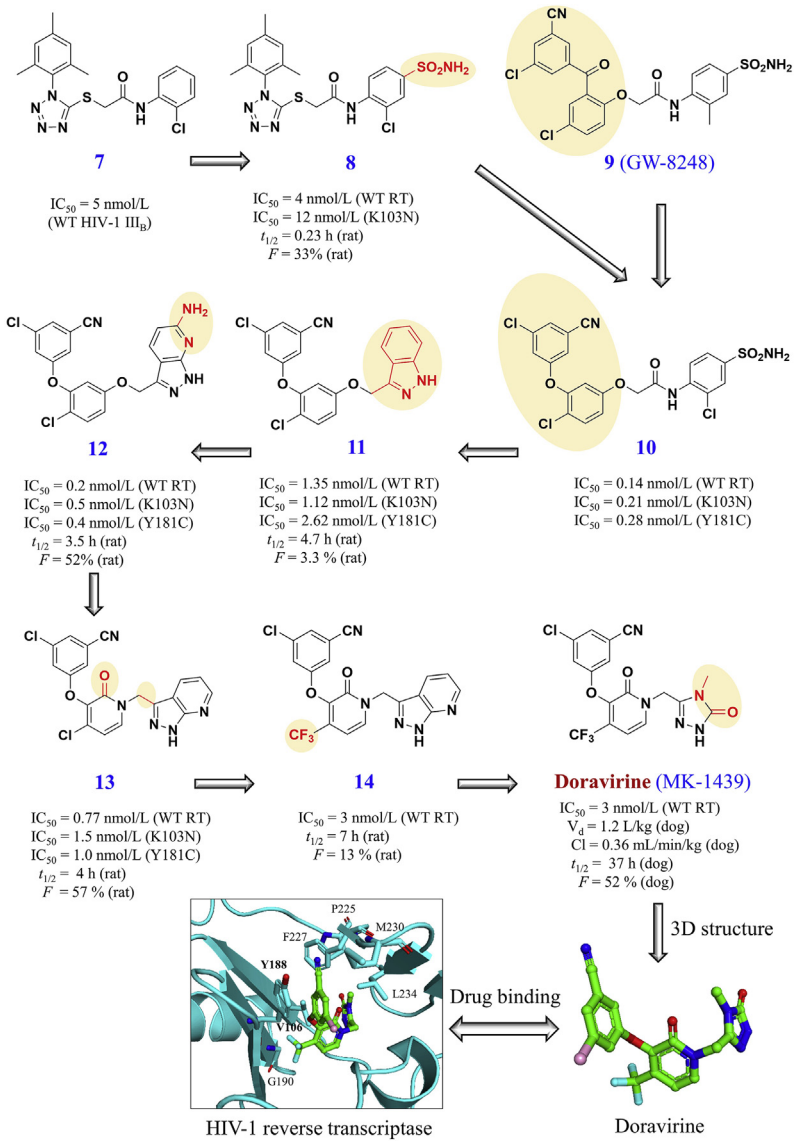

Figure 6 Discovery of doravirine based on a template of the lead tetrazole thioacetanilide inhibitor **7**. Drug binding pocket of rilpivirine is highlighted in HIV-1 reverse transcriptase (PDB code: 4NCG). Amino acid positions with known resistant residues are highlighted.

(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)[115]. 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[119]. Moreover, azvudine is mainly metabolized by CYP3A[120], 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 pre-clinical study[122]. 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_{max}: 0.15 ± 0.04 days, C_{max}: 98 ± 74.3 ng/mL, and AUC_{inf}: 829 ± 507 ng·h/mL[122]. 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_{max}: 6.3 ± 0.5 days, (iii) C_{max}: 148 ± 8 ng/mL, and (iv) AUC_{inf}: 2123 ± 266 ng·h/mL[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[123]. In treatment-naïve 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 elsulfavirine arm (74%, 35/47)[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-naïve patients who continued the treatment of elsulfavirine 20 mg plus TDF + FTC[124]. The drug-associated adverse events were reported in 23.3% (14/60)[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[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[129]; and (iv) apricitabine was discontinued in 2016 due to a lack of funding and interests from its sponsor. Here, we summarize the recent development of three NRTIs (islatravir, MK-8504, MK-8583) and three NNRTIs (MK-8507, IQP-0528, MIV-150) that have been evaluated by phase one clinical trials.

9.1. *Islatravir (MK-8591, EFdA)*

Islatravir, 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[130−133]. Unlike the conventional chain-terminating NRTIs, islatravir acts as an effective immediate or delayed chain terminator depending on the sequence of the nucleic acid substrate[134]. The biocatalytic cascade synthesis of islatravir could be efficiently made by five engineered enzymes with four auxiliary enzymes[135]. Islatravir offers potent antiviral activities (EC_{50} ≤ 11 nmol/L) against broad-spectrum viral isolates with multi-drug resistant mutations (*e.g.*, K65R, Q151M, M184V)[133]. The EC_{50} values of islatravir were less than 21 nmol/L against a variety of HIV-1 strains (*e.g.*, HIV-1_{NL4-3}, HIV-1_{MDR}, HIV-1_{Ba-L})[136]. In cell-based assays, an apparent synergism of islatravir plus rilpivirine may enhance the antiviral and prophylactic activity against HIV-1[137]. Pharmacokinetics features such as C_{max}: 3.2 nmol/mL, T_{max}: 0.5 h, and $AUC_{12\ h}$: 9.5 nmol/h/mL were measured after the oral administration of islatravir in 25 humanized mice infected with HIV-1_{NL4-3}[138].

The once-weekly oral dosing of islatravir (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[139]. A single subcutaneous administration of islatravir-eluting implants in rodents and rhesus macaques sustained the drug release at clinically relevant concentrations for at least 6 months[140]. In a phase one study (NCT02217904), a single dose of islatravir 0.5 mg suppressed HIV-1 RNA levels by more than one log on Day 7 in 30 treatment-naïve adults[141]. The prophylaxis activity of islatravir 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[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_{max}: 0.5 h) and eliminated from plasma[142]. Both compounds were well-tolerated with only mild to moderate adverse events[142]. 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[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[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_{max}: 2.0 h, C_{max}: 2.11 μmol/L and $AUC_{0\text{-}inf}$: 129 μmol/L·h[145]. *In vitro* IC_{50} of MK-8507 was 51.3 nmol/L based on the Monogram's PhenoSense assay[145]. Moreover, MK-8507 maintained the *in vitro* potency against NNRTI resistant-associated variants such as K103N, Y181C and G190A[145]. A phase 2 study (NCT04564547) was planned to evaluate the once-weekly two-drug regimen of MK-8507 (100, 200, 400 mg) plus islatravir 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[146]. A dual chamber vaginal/rectal microbicide gel called DuoGel™ inhibited the CCR5-tropic subtype B strain HIV-$1_{US/92/727}$ with the EC_{50} values of 4.11−4.79 nmol/L[147]. IQP-0528 gel is a

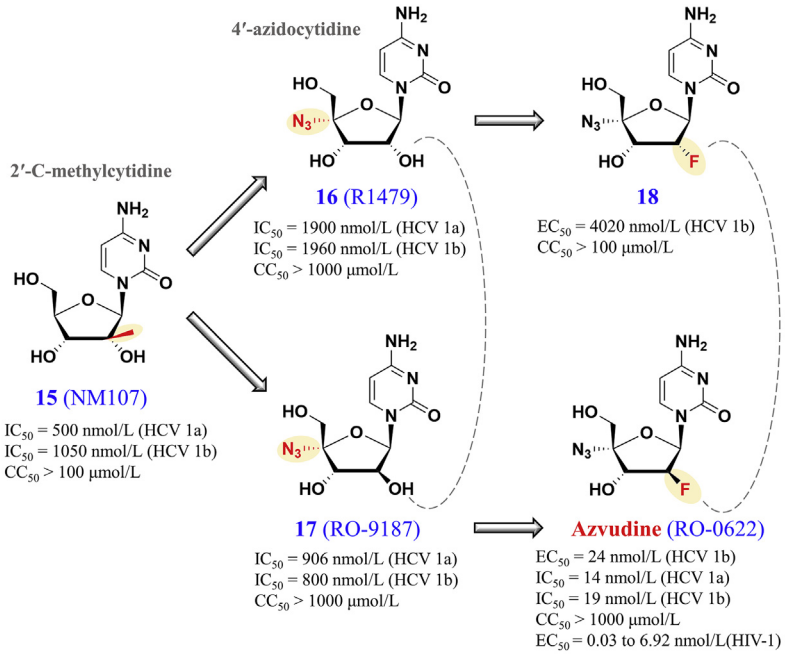

Figure 7 Discovery of azvudine. Synthesis pathways and *in vitro* results can be found in Refs. 112−115.

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[148]. 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[149].

9.5. MIV-150

MIV-150 (Fig. 8B) is a novel NNRTI with antiviral activities against HIV-1 replications[73]. Although the oral use of MIV-150 was discontinued because of its poor systemic absorption and rapid systemic clearance[150], 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

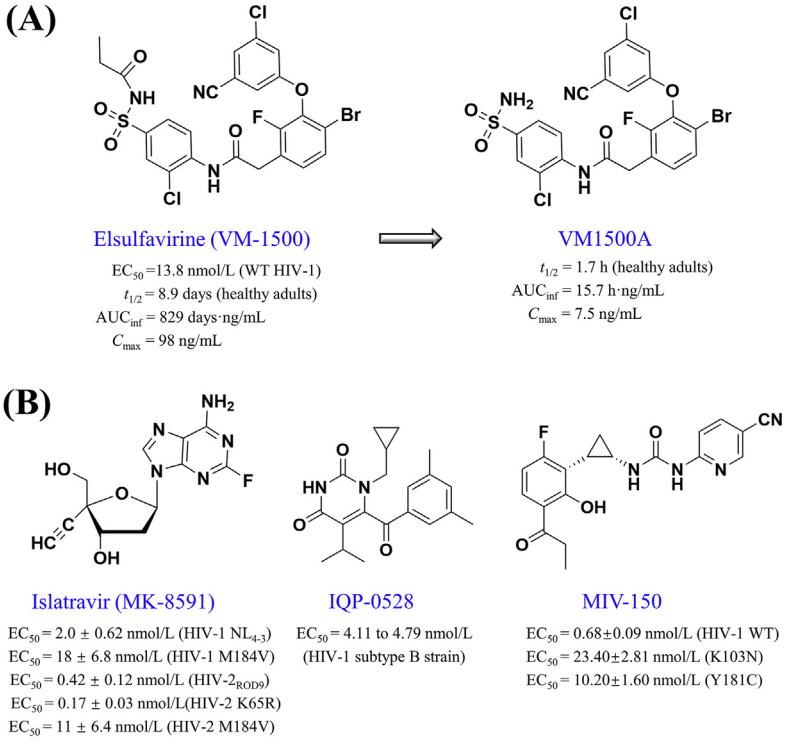

Figure 8 Chemical structures of elsulfavirine, islatravir, IQP-0528, and MIV-150.

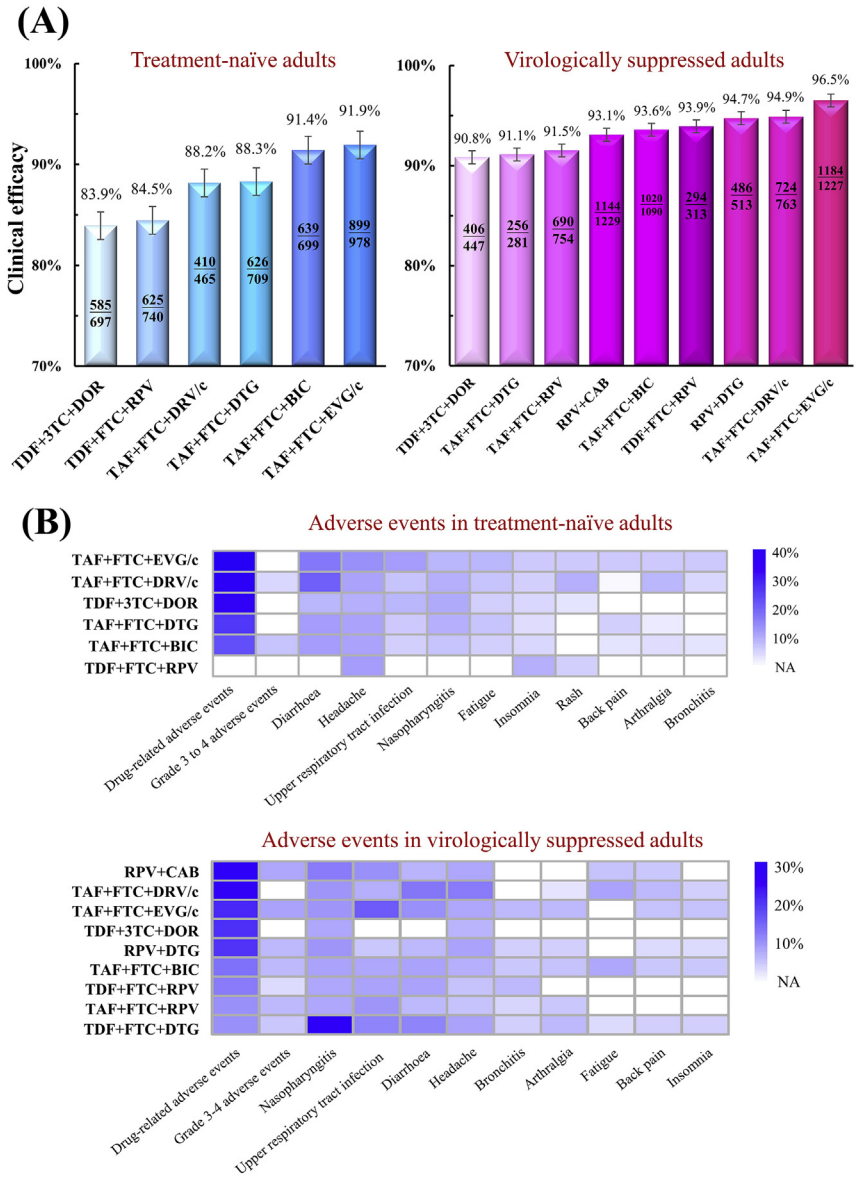

Figure 9 Efficacy and safety of approved antiretroviral regimens in the treatment of treatment-naïve and virologically-suppressed adults with HIV-1 infections. (A) Clinical efficacy was defined by the proportion of patients achieving HIV-1 RNA <50 copies/mL at Week 48. Data from Tables 3 and 4 were merged to demonstrate the clinical efficacy of approved antiretroviral regimens. (B) Proportions of adverse events during the treatment of approved antiretroviral regimens in randomized clinical trials. Missing data are indicated by white-colored cells. Original data are available in Table S1.

papillomavirus; and (iii) MIV-150 plus levonorgestrel to prevent the HIV-1, HSV-2, human papillomavirus, and unintended pregnancy[151]. 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[152]. 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[153]. 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 (89.5%, 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 + 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[154]. NNRTIs are now gradually replaced by HIV integrase inhibitors in the first-line combination regimens according to the IAS-USA and the EACS guidelines[10,11]. First, NNRTIs are only limited to the treatment of HIV-1 but not HIV-2[1]. Second, many NNRTIs have clinically significant drug−drug and drug−food interactions since they are the substrates (*e.g.*, doravirine, rilpivirine) or inducers (*e.g.*, efavirenz) of cytochrome P450 3A4 (CYP3A4)−an important oxidizing enzyme in humans. Third, NNRTIs usually have low genetic barriers to resistance and there is an increasing prevalence of NNRTI-associated transmitted drug resistance in treatment-naïve patients from North America, Latin America/Caribbean, Sub-Saharan Africa, South/Southeast Asia, and Upper-Income Asian Countries[155]. Fourth, transmitted NNRTI resistance before first-line treatment is potentially associated with the long-term failure of first-line regimens containing integrase inhibitors such as dolutegravir[156]. Fifth, NNRTIs may cause neuropsychiatric adverse effects and these drug-related adverse effects should be closely monitored in clinical practice[157].

Despite the success of many approved RT inhibitors, HIV strains evolve fast especially under the drug selective pressure[158,159] and mutated residues near the drug-binding pocket of HIV RT may reduce the drug-target binding affinity[5]. To encounter emerging drug resistance mutations, many strategies have been proposed to develop the next generation of RT inhibitors with better drug resistance profiles[5,6,8,160]. (i) Multi-target strategy that designs novel RT inhibitors to target evolutionarily conserved binding pockets, divalent metal binding pockets, the substrate-envelope pocket, and/or the RNase H domain[8]. (ii) Conformation-based strategy that designs novel RT inhibitors with conformational flexibility to target ever-changing binding pockets with multiple drug positioning, covalent bonding, multivalent binding, and van der Waals forces[5,6,8,161]. (iii) RT inhibitors without overlapping resistance profiles could be combined to act synergistically for the maximize suppression against diverse strains of the highly mutable HIV[5,6,8]. Additionally, novel antiretroviral agents such as lenacapavir (GS-6207) that targets the viral capsid[162] may provide alternative options in the long-acting fixed-dose regimens.

HIV RT inhibitors can be repurposed for the treatment of other human diseases. (i) Three NRTIs (TAF, TDF, lamivudine) have also been approved and recommended for the treatment of HBV infections[163−165]. (ii) Anti-inflammasome NRTIs such as lamivudine may improve insulin sensitivity and prevent the development of type two diabetes[166]. (iii) NRTIs may reduce the risk of age-related macular degeneration that causes blindness in humans[167]. (iv) NRTIs such as lamivudine might be repurposed as anti-cancer drugs[168]. (v) HIV RT inhibitors have been initially proposed to treat coronavirus disease 2019 (COVID-19)[168,169], which has caused a global pandemic with severe morbidity and mortality since the end of 2019[170−174]. As of today, no anti-HIV drug has been approved for the treatment of COVID-19[175], whereas TDF + FTC could reduce the risk of COVID-19 and hospitalization in HIV-positive patients[176].

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 application; (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[177]. In the foreseeable future, antiretroviral regimens will still 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.

References

1. De Clercq E, Li G. Approved antiviral drugs over the past 50 years. *Clin Microbiol Rev* 2016;**29**:695–747.
2. De Clercq E. Fifty years in search of selective antiviral drugs. *J Med Chem* 2019;**62**:7322–39.
3. De Clercq E. Role of tenofovir alafenamide (TAF) in the treatment and prophylaxis of HIV and HBV infections. *Biochem Pharmacol* 2018;**153**:2–11.
4. Wang Y, De Clercq E, Li G. Current and emerging non-nucleoside reverse transcriptase inhibitors (NNRTIs) for HIV-1 treatment. *Expet Opin Drug Metabol Toxicol* 2019;**15**:813–29.
5. Ma Y, Frutos-Beltran E, Kang D, Pannecouque C, De Clercq E, Menendez-Arias L, et al. Medicinal chemistry strategies for discovering antivirals effective against drug-resistant viruses. *Chem Soc Rev* 2021;**50**:4514–40.
6. Zhuang C, Pannecouque C, De Clercq E, Chen F. Development of non-nucleoside reverse transcriptase inhibitors (NNRTIs): our past twenty years. *Acta Pharm Sin B* 2020;**10**:961–78.
7. Song L, Ding S, Ge Z, Zhu X, Qiu C, Wang Y, et al. Nucleoside/-nucleotide reverse transcriptase inhibitors attenuate angiogenesis and lymphangiogenesis by impairing receptor tyrosine kinases signalling in endothelial cells. *Br J Pharmacol* 2018;**175**:1241–59.
8. Cilento ME, Kirby KA, Sarafianos SG. Avoiding drug resistance in HIV reverse transcriptase. *Chem Rev* 2021;**121**:3271–96.
9. Ha B, Larsen KP, Zhang J, Fu Z, Montabana E, Jackson LN, et al. High-resolution view of HIV-1 reverse transcriptase initiation complexes and inhibition by NNRTI drugs. *Nat Commun* 2021;**12**:2500.
10. Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA Panel. *J Am Med Assoc* 2020;**324**:1651–69.
11. Ryom L, Cotter A, De Miguel R, Beguelin C, Podlekareva D, Arribas JR, et al. 2019 update of the European AIDS Clinical Society Guidelines for treatment of people living with HIV version 10.0. *HIV Med* 2020;**21**:617–24.
12. Gu SX, Xiao T, Zhu YY, Liu GY, Chen F. Recent progress in HIV-1 inhibitors targeting the entrance channel of HIV-1 non-nucleoside reverse transcriptase inhibitor binding pocket. *Eur J Med Chem* 2019;**174**:277–91.
13. Wang L, Sarafianos SG, Wang Z. Cutting into the substrate dominance: pharmacophore and structure-based approaches toward inhibiting human immunodeficiency virus reverse transcriptase-associated ribonuclease H. *Acc Chem Res* 2020;**53**:218–30.
14. Shin YH, Park CM, Yoon CH. An overview of human immunodeficiency virus-1 antiretroviral drugs: general principles and current status. *Infect Chemother* 2021;**53**:29–45.
15. Marcus JL, Neugebauer RS, Leyden WA, Chao CR, Xu L, Quesenberry CPJ, et al. Use of abacavir and risk of cardiovascular disease among HIV-infected individuals. *J Acquir Immune Defic Syndr* 2016;**71**:413–9.
16. Dalwadi DA, Ozuna L, Harvey BH, Viljoen M, Schetz JA. Adverse neuropsychiatric events and recreational use of efavirenz and other HIV-1 antiretroviral drugs. *Pharmacol Rev* 2018;**70**:684–711.
17. Casado JL. Renal and bone toxicity with the use of tenofovir: understanding at the end. *AIDS Rev* 2016;**18**:59–68.
18. Li G, Xu M, Yue T, Gu W, Tan L. Life-long passion for antiviral research and drug development: 80th birthday of Prof. Dr. Erik De Clercq. *Biochem Pharmacol* 2021;**185**:114485.
19. Li G, Yue T, Zhang P, Gu W, Gao LJ, Tan L. Drug discovery of nucleos(t)ide antiviral agents: dedicated to Prof. Dr. Erik De Clercq on occasion of his 80th birthday. *Molecules* 2021;**26**:923.
20. Hendrix CW. HIV Antiretroviral pre-exposure prophylaxis: development challenges and pipeline promise. *Clin Pharmacol Ther* 2018;**104**:1082–97.
21. Slagman S, Fessner WD. Biocatalytic routes to anti-viral agents and their synthetic intermediates. *Chem Soc Rev* 2021;**50**:1968–2009.
22. Vanangamudi M, Kurup S, Namasivayam V. Non-nucleoside reverse transcriptase inhibitors (NNRTIs): a brief overview of clinically approved drugs and combination regimens. *Curr Opin Pharmacol* 2020;**54**:179–87.
23. Gu SX, Zhu YY, Wang C, Wang HF, Liu GY, Cao S, et al. Recent discoveries in HIV-1 reverse transcriptase inhibitors. *Curr Opin Pharmacol* 2020;**54**:166–72.
24. Miao M, De Clercq E, Li G. Clinical significance of chemokine receptor antagonists. *Expet Opin Drug Metabol Toxicol* 2020;**16**:11–30.
25. Wensing AM, Calvez V, Ceccherini-Silberstein F, Charpentier C, Gunthard HF, Paredes R, et al. 2019 update of the drug resistance mutations in HIV-1. *Top Antivir Med* 2019;**27**:111–21.
26. Zhang M, Li G, Shang J, Pan C, Zhang M, Yin Z, et al. Rapidly decreased HBV RNA predicts responses of pegylated interferons in HBeAg-positive patients: a longitudinal cohort study. *Hepatol Int* 2020;**14**:212–24.
27. Li G, De Clercq E. Current therapy for chronic hepatitis C: the role of direct-acting antivirals. *Antivir Res* 2017;**142**:83–122.
28. Miao M, Jing X, De Clercq E, Li G. Danoprevir for the treatment of hepatitis C virus infection: design, development, and place in therapy. *Drug Des Dev Ther* 2020;**14**:2759–74.
29. Balzarini J, Holý A, Jindrich J, Naesens L, Snoeck R, Schols D, et al. Differential antiherpesvirus and antiretrovirus effects of the (*S*) and (*R*) enantiomers of acyclic nucleoside phosphonates: potent and selective *in vitro* and *in vivo* antiretrovirus activities of (*R*)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine. *Antimicrob Agents Chemother* 1993;**37**:332–8.
30. Ying C, De Clercq E, Neyts J. Lamivudine, adefovir and tenofovir exhibit long-lasting anti-hepatitis B virus activity in cell culture. *J Viral Hepat* 2000;**7**:79–83.
31. Cundy KC, Sueoka C, Lynch GR, Griffin L, Lee WA, Shaw JP. Pharmacokinetics and bioavailability of the anti-human immunodeficiency virus nucleotide analog 9-[(*R*)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs. *Antimicrob Agents Chemother* 1998;**42**:687–90.
32. Deeks SG, Barditch-Crovo P, Lietman PS, Hwang F, Cundy KC, Rooney JF, et al. Safety, pharmacokinetics, and antiretroviral activity of intravenous 9-[2-(*R*)-(phosphonomethoxy)propyl]adenine, a novel anti-human immunodeficiency virus (HIV) therapy, in HIV-infected adults. *Antimicrob Agents Chemother* 1998;**42**:2380–4.
33. Cihlar T. Nucleotide HIV reverse transcriptase inhibitors: tenofovir and beyond. *Curr Opin HIV AIDS* 2006;**1**:373–9.
34. Serpi M, Pertusati F. An overview of ProTide technology and its implications to drug discovery. *Expet Opin Drug Discov* 2021;**16**:1149–61.
35. Mehellou Y, Rattan HS, Balzarini J. The ProTide prodrug technology: from the concept to the clinic. *J Med Chem* 2018;**61**:2211–26.
36. Chapman H, Kernan M, Rohloff J, Sparacino M, Terhorst T. Purification of PMPA amidate prodrugs by SMB chromatography and X-ray crystallography of the diastereomerically pure GS-7340. *Nucleos Nucleot Nucleic Acids* 2001;**20**:1085–90.
37. Chapman H, Kernan M, Prisbe E, Rohloff J, Sparacino M, Terhorst T, et al. Practical synthesis, separation, and stereochemical assignment of the PMPA pro-drug GS-7340. *Nucleos Nucleot Nucleic Acids* 2001;**20**:621–8.
38. Lee WA, He GX, Eisenberg E, Cihlar T, Swaminathan S, Mulato A, et al. Selective intracellular activation of a novel prodrug of the human immunodeficiency virus reverse transcriptase inhibitor

tenofovir leads to preferential distribution and accumulation in lymphatic tissue. *Antimicrob Agents Chemother* 2005;**49**:1898–906.
39. Callebaut C, Stepan G, Tian Y, Miller MD. *In vitro* virology profile of tenofovir alafenamide, a novel oral prodrug of tenofovir with improved antiviral activity compared to that of tenofovir disoproxil fumarate. *Antimicrob Agents Chemother* 2015;**59**:5909–16.
40. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide *versus* tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 2015;**385**:2606–15.
41. Wang H, Lu X, Yang X, Xu N. The efficacy and safety of tenofovir alafenamide *versus* tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: meta-analysis. *Medicine (Baltim)* 2016;**95**:e5146.
42. Fletcher CV, Podany AT, Thorkelson A, Winchester LC, Mykris T, Anderson J, et al. The lymphoid tissue pharmacokinetics of tenofovir disoproxil fumarate and tenofovir alafenamide in HIV-infected persons. *Clin Pharmacol Ther* 2020;**108**:971–5.
43. Ruane PJ, DeJesus E, Berger D, Markowitz M, Bredeek UF, Callebaut C, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J Acquir Immune Defic Syndr* 2013;**63**:449–55.
44. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. *Mol Pharm* 2013;**10**:459–66.
45. Custodio JM, Fordyce M, Garner W, Vimal M, Ling KH, Kearney BP, et al. Pharmacokinetics and safety of tenofovir alafenamide in HIV-uninfected subjects with severe renal impairment. *Antimicrob Agents Chemother* 2016;**60**:5135–40.
46. Begley R, Das M, Zhong L, Ling J, Kearney BP, Custodio JM. Pharmacokinetics of tenofovir alafenamide when coadministered with other HIV antiretrovirals. *J Acquir Immune Defic Syndr* 2018;**78**:465–72.
47. Lepist EI, Phan TK, Roy A, Tong L, Maclennan K, Murray B, et al. Cobicistat boosts the intestinal absorption of transport substrates, including HIV protease inhibitors and GS-7340, *in vitro*. *Antimicrob Agents Chemother* 2012;**56**:5409–13.
48. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide *versus* tenofovir disoproxil fumarate: is there a true difference in efficacy and safety?. *J Virus Erad* 2018;**4**:72–9.
49. Funderburg NT, McComsey GA, Kulkarni M, Bannerman T, Mantini J, Thornton B, et al. Equivalent decline in inflammation markers with tenofovir disoproxil fumarate *vs.* tenofovir alafenamide. *EBioMedicine* 2016;**13**:321–7.
50. Mayer KH, Molina JM, Thompson MA, Anderson PL, Mounzer KC, De Wet JJ, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet* 2020;**396**:239–54.
51. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;**363**:2587–99.
52. Acosta RK, Chen GQ, Chang S, Martin R, Wang X, Huang H, et al. Three-year study of pre-existing drug resistance substitutions and efficacy of bictegravir/emtricitabine/tenofovir alafenamide in HIV-1 treatment-naive participants. *J Antimicrob Chemother* 2021;**76**:2153–7.
53. Pozniak A, Arribas JR, Gathe J, Gupta SK, Post FA, Bloch M, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48-week results from a single-arm, multicenter, open-label phase 3 study. *J Acquir Immune Defic Syndr* 2016;**71**:530–7.
54. Eron Jr JJ, Lelievre JD, Kalayjian R, Slim J, Wurapa AK, Stephens JL, et al. Safety of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in HIV-1-infected adults with end-stage renal disease on chronic haemodialysis: an open-label, single-arm, multicentre, phase 3b trial. *Lancet HIV* 2018;**6**:e15–24.
55. Margot NA, Wong P, Kulkarni R, White K, Porter D, Abram ME, et al. Commonly transmitted HIV-1 drug resistance mutations in reverse-transcriptase and protease in antiretroviral treatment-naive patients and response to regimens containing tenofovir disoproxil fumarate or tenofovir alafenamide. *J Infect Dis* 2017;**215**:920–7.
56. Margot N, Cox S, Das M, McCallister S, Miller MD, Callebaut C. Rare emergence of drug resistance in HIV-1 treatment-naive patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide for 144 weeks. *J Clin Virol* 2018;**103**:37–42.
57. Pauwels R, Andries K, Debyser Z, Van Daele P, Schols D, Stoffels P, et al. Potent and highly selective human immunodeficiency virus type 1 (HIV-1) inhibition by a series of alpha-anilinophenylacetamide derivatives targeted at HIV-1 reverse transcriptase. *Proc Natl Acad Sci U S A* 1993;**90**:1711–5.
58. Ludovici DW, Kukla MJ, Grous PG, Krishnan S, Andries K, de Bethune MP, et al. Evolution of anti-HIV drug candidates. Part 1: from alpha-anilinophenylacetamide (alpha-APA) to imidoyl thiourea (ITU). *Bioorg Med Chem Lett* 2001;**11**:2225–8.
59. Ludovici DW, Kavash RW, Kukla MJ, Ho CY, Ye H, De Corte BL, et al. Evolution of anti-HIV drug candidates. Part 2: diaryltriazine (DATA) analogues. *Bioorg Med Chem Lett* 2001;**11**:2229–34.
60. Ludovici DW, De Corte BL, Kukla MJ, Ye H, Ho CY, Lichtenstein MA, et al. Evolution of anti-HIV drug candidates. Part 3: diarylpyrimidine (DAPY) analogues. *Bioorg Med Chem Lett* 2001;**11**:2235–9.
61. De Clercq E. An Odyssey in antiviral drug development-50 years at the Rega Institute: 1964–2014. *Acta Pharm Sin B* 2015;**5**:520–43.
62. Janssen PA, Lewi PJ, Arnold E, Daeyaert F, de Jonge M, Heeres J, et al. In search of a novel anti-HIV drug: multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (R278474, rilpivirine). *J Med Chem* 2005;**48**:1901–9.
63. Van Herrewege Y, Michiels J, Van Roey J, Fransen K, Kestens L, Balzarini J, et al. *In vitro* evaluation of nonnucleoside reverse transcriptase inhibitors UC-781 and TMC120-R147681 as human immunodeficiency virus microbicides. *Antimicrob Agents Chemother* 2004;**48**:337–9.
64. Andries K, Azijn H, Thielemans T, Ludovici D, Kukla M, Heeres J, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother* 2004;**48**:4680–6.
65. Malcolm RK, Woolfson AD, Toner CF, Morrow RJ, McCullagh SD. Long-term, controlled release of the HIV microbicide TMC120 from silicone elastomer vaginal rings. *J Antimicrob Chemother* 2005;**56**:954–6.
66. Chen BA, Panther L, Marzinke MA, Hendrix CW, Hoesley CJ, van der Straten A, et al. Phase 1 safety, pharmacokinetics, and pharmacodynamics of dapivirine and maraviroc vaginal rings: a double-blind randomized trial. *J Acquir Immune Defic Syndr* 2015;**70**:242–9.
67. Devlin B, Nuttall J, Wilder S, Woodsong C, Rosenberg Z. Development of dapivirine vaginal ring for HIV prevention. *Antivir Res* 2013;**100**(Suppl):S3–8.
68. Romano J, Variano B, Coplan P, Van Roey J, Douville K, Rosenberg Z, et al. Safety and availability of dapivirine (TMC120) delivered from an intravaginal ring. *AIDS Res Hum Retrovir* 2009;**25**:483–8.
69. Baeten JM, Hendrix CW, Hillier SL. Topical microbicides in HIV prevention: state of the promise. *Annu Rev Med* 2020;**71**:361–77.
70. Van Herrewege Y, Vanham G, Michiels J, Fransen K, Kestens L, Andries K, et al. A series of diaryltriazines and diarylpyrimidines are highly potent nonnucleoside reverse transcriptase inhibitors with possible applications as microbicides. *Antimicrob Agents Chemother* 2004;**48**:3684–9.
71. Nel A, Smythe S, Young K, Malcolm K, McCoy C, Rosenberg Z, et al. Safety and pharmacokinetics of dapivirine delivery from matrix

and reservoir intravaginal rings to HIV-negative women. *J Acquir Immune Defic Syndr* 2009;**51**:416−23.
72. Nel A, Haazen W, Nuttall J, Romano J, Rosenberg Z, van Niekerk N. A safety and pharmacokinetic trial assessing delivery of dapivirine from a vaginal ring in healthy women. *AIDS* 2014;**28**:1479−87.
73. Giacobbi NS, Sluis-Cremer N. *In vitro* cross-resistance profiles of rilpivirine, dapivirine, and MIV-150, nonnucleoside reverse transcriptase inhibitor microbicides in clinical development for the prevention of HIV-1 infection. *Antimicrob Agents Chemother* 2017;**61**. e00277-17.
74. Penrose KJ, Wallis CL, Brumme CJ, Hamanishi KA, Gordon KC, Viana RV, et al. Frequent cross-resistance to dapivirine in HIV-1 subtype C-infected individuals after first-line antiretroviral therapy failure in South Africa. *Antimicrob Agents Chemother* 2017;**61**: e01805−16.
75. Schader SM, Oliveira M, Ibanescu RI, Moisi D, Colby-Germinario SP, Wainberg MA. *In vitro* resistance profile of the candidate HIV-1 microbicide drug dapivirine. *Antimicrob Agents Chemother* 2012;**56**:751−6.
76. Thompson M, Orkin C, Molina JM, Sax P, Cahn P, Squires K, et al. Once-daily doravirine for initial treatment of adults living with human immunodeficiency virus-1: an integrated safety analysis. *Clin Infect Dis* 2020;**70**:1336−43.
77. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med* 2016;**375**: 2121−32.
78. Nel A, van Niekerk N, Kapiga S, Bekker LG, Gama C, Gill K, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *N Engl J Med* 2016;**375**:2133−43.
79. Baeten JM, Palanee-Phillips T, Mgodi NM, Mayo AJ, Szydlo DW, Ramjee G, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. *Lancet HIV* 2021;**8**:e87−95.
80. Reddy K, Kelly C, Brown ER, Jeenarain N, Naidoo L, Siva S, et al. Use of the dapivirine vaginal ring and effect on cervical cytology abnormalities. *AIDS* 2020;**34**:559−67.
81. Nel A, van Niekerk N, Van Baelen B, Malherbe M, Mans W, Carter A, et al. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. *Lancet HIV* 2021;**8**:e77−86.
82. Guillemont J, Pasquier E, Palandjian P, Vernier D, Gaurrand S, Lewi PJ, et al. Synthesis of novel diarylpyrimidine analogues and their antiviral activity against human immunodeficiency virus type 1. *J Med Chem* 2005;**48**:2072−9.
83. Azijn H, Tirry I, Vingerhoets J, de Béthune MP, Kraus G, Boven K, et al. TMC278, a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), active against wild-type and NNRTI-resistant HIV-1. *Antimicrob Agents Chemother* 2010;**54**:718−27.
84. Mordant C, Schmitt B, Pasquier E, Demestre C, Queguiner L, Masungi C, et al. Synthesis of novel diarylpyrimidine analogues of TMC278 and their antiviral activity against HIV-1 wild-type and mutant strains. *Eur J Med Chem* 2007;**42**:567−79.
85. Goebel F, Yakovlev A, Pozniak AL, Vinogradova E, Boogaerts G, Hoetelmans R, et al. Short-term antiviral activity of TMC278—a novel NNRTI—in treatment-naive HIV-1-infected subjects. *AIDS* 2006;**20**:1721−6.
86. van 't Klooster G, Hoeben E, Borghys H, Looszova A, Bouche MP, van Velsen F, et al. Pharmacokinetics and disposition of rilpivirine (TMC278) nanosuspension as a long-acting injectable antiretroviral formulation. *Antimicrob Agents Chemother* 2010;**54**:2042−50.
87. Letendre SL, Mills A, Hagins D, Swindells S, Felizarta F, Devente J, et al. Pharmacokinetics and antiviral activity of cabotegravir and rilpivirine in cerebrospinal fluid following long-acting injectable administration in HIV-infected adults. *J Antimicrob Chemother* 2020; **75**:648−55.
88. Llibre JM, Hung CC, Brinson C, Castelli F, Girard PM, Kahl LP, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* 2018;**391**:839−49.
89. Orkin C, Oka S, Philibert P, Brinson C, Bassa A, Gusev D, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. *Lancet HIV* 2021;**8**:e185−96.
90. Muraglia E, Kinzel OD, Laufer R, Miller MD, Moyer G, Munshi V, et al. Tetrazole thioacetanilides: potent non-nucleoside inhibitors of WT HIV reverse transcriptase and its K103N mutant. *Bioorg Med Chem Lett* 2006;**16**:2748−52.
91. Tucker TJ, Saggar S, Sisko JT, Tynebor RM, Williams TM, Felock PJ, et al. The design and synthesis of diaryl ether second generation HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) with enhanced potency *versus* key clinical mutations. *Bioorg Med Chem Lett* 2008;**18**:2959−66.
92. Tucker TJ, Sisko JT, Tynebor RM, Williams TM, Felock PJ, Flynn JA, et al. Discovery of 3-{5-[(6-amino-1*H*-pyrazolo[3,4-*b*] pyridine-3-yl)methoxy]-2-chlorophenoxy}-5-chloro benzonitrile (MK-4965): a potent, orally bioavailable HIV-1 non-nucleoside reverse transcriptase inhibitor with improved potency against key mutant viruses. *J Med Chem* 2008;**51**:6503−11.
93. Gomez R, Jolly S, Williams T, Tucker T, Tynebor R, Vacca J, et al. Design and synthesis of pyridone inhibitors of non-nucleoside reverse transcriptase. *Bioorg Med Chem Lett* 2011;**21**:7344−50.
94. Cote B, Burch JD, Asante-Appiah E, Bayly C, Bedard L, Blouin M, et al. Discovery of MK-1439, an orally bioavailable non-nucleoside reverse transcriptase inhibitor potent against a wide range of resistant mutant HIV viruses. *Bioorg Med Chem Lett* 2014;**24**:917−22.
95. Feng M, Sachs NA, Xu M, Grobler J, Blair W, Hazuda DJ, et al. Doravirine suppresses common nonnucleoside reverse transcriptase inhibitor-associated mutants at clinically relevant concentrations. *Antimicrob Agents Chemother* 2016;**60**:2241−7.
96. Lai MT, Feng M, Falgueyret JP, Tawa P, Witmer M, DiStefano D, et al. *In vitro* characterization of MK-1439, a novel HIV-1 non-nucleoside reverse transcriptase inhibitor. *Antimicrob Agents Chemother* 2014;**58**:1652−63.
97. Feng M, Wang D, Grobler JA, Hazuda DJ, Miller MD, Lai MT. *In vitro* resistance selection with doravirine (MK-1439), a novel nonnucleoside reverse transcriptase inhibitor with distinct mutation development pathways. *Antimicrob Agents Chemother* 2015;**59**: 590−8.
98. Smith SJ, Pauly GT, Akram A, Melody K, Ambrose Z, Schneider JP, et al. Rilpivirine and doravirine have complementary efficacies against NNRTI-resistant HIV-1 mutants. *J Acquir Immune Defic Syndr* 2016;**72**:485−91.
99. Soulie C, Santoro MM, Charpentier C, Storto A, Paraskevis D, Di Carlo D, et al. Rare occurrence of doravirine resistance-associated mutations in HIV-1-infected treatment-naive patients. *J Antimicrob Chemother* 2019;**74**:614−7.
100. Sterrantino G, Borghi V, Callegaro AP, Bruzzone B, Saladini F, Maggiolo F, et al. Prevalence of predicted resistance to doravirine in HIV-1-positive patients after exposure to non-nucleoside reverse transcriptase inhibitors. *Int J Antimicrob Agents* 2019;**53**:515−9.
101. Yee KL, Ouerdani A, Claussen A, de Greef R, Wenning L. Population pharmacokinetics of doravirine and exposure-response analysis in individuals with HIV-1. *Antimicrob Agents Chemother* 2019;**63**: e02502−18.
102. Ankrom W, Yee KL, Sanchez RI, Adedoyin A, Fan L, Marbury T, et al. Severe renal impairment has minimal impact on doravirine pharmacokinetics. *Antimicrob Agents Chemother* 2018;**62**:e00326-18.
103. Khalilieh S, Yee KL, Liu R, Fan L, Sanchez RI, Auger P, et al. Moderate hepatic impairment does not affect doravirine pharmacokinetics. *J Clin Pharmacol* 2017;**57**:777−83.
104. Anderson MS, Gilmartin J, Cilissen C, De Lepeleire I, Van Bortel L, Dockendorf MF, et al. Safety, tolerability and pharmacokinetics of doravirine, a novel HIV non-nucleoside reverse transcriptase

inhibitor, after single and multiple doses in healthy subjects. *Antivir Ther* 2015;**20**:397–405.
105. Sanchez RI, Fillgrove KL, Yee KL, Liang Y, Lu B, Tatavarti A, et al. Characterisation of the absorption, distribution, metabolism, excretion and mass balance of doravirine, a non-nucleoside reverse transcriptase inhibitor in humans. *Xenobiotica* 2019;**49**:422–32.
106. Bleasby K, Fillgrove KL, Houle R, Lu B, Palamanda J, Newton DJ, et al. *In vitro* evaluation of the drug interaction potential of doravirine. *Antimicrob Agents Chemother* 2019;**63**:e02492-18.
107. Khalilieh SG, Yee KL, Sanchez RI, Fan L, Anderson MS, Sura M, et al. Doravirine and the potential for CYP3A-mediated drug–drug interactions. *Antimicrob Agents Chemother* 2019;**63**:e02016–8.
108. Ankrom W, Sanchez RI, Yee KL, Fan L, Mitra P, Wolford D, et al. Investigation of pharmacokinetic interactions between doravirine and elbasvir-grazoprevir and ledipasvir-sofosbuvir. *Antimicrob Agents Chemother* 2019;**63**:e02491-18.
109. Anderson MS, Gilmartin J, Fan L, Yee KL, Kraft WK, Triantafyllou I, et al. No meaningful drug interactions with doravirine, lamivudine and tenofovir disoproxil fumarate coadministration. *Antivir Ther* 2019;**24**:443–50.
110. Wong A, Goldstein D, Mallolas J, DeJesus E, Johnson M, Molina JM, et al. Efficacy and safety of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) in treatment-naive adults with HIV-1 and transmitted nonnucleoside reverse transcriptase inhibitor resistance mutations. *J Acquir Immune Defic Syndr* 2019;**82**:e47–9.
111. Molina JM, Yazdanpanah Y, Afani Saud A, Bettacchi C, Chahin Anania C, DeJesus E, et al. Islatravir in combination with doravirine for treatment-naive adults with HIV-1 infection receiving initial treatment with islatravir, doravirine, and lamivudine: a phase 2b, randomised, double-blind, dose-ranging trial. *Lancet HIV* 2021;**8**:e324–33.
112. Smith DB, Martin JA, Klumpp K, Baker SJ, Blomgren PA, Devos R, et al. Design, synthesis, and antiviral properties of 4′-substituted ribonucleosides as inhibitors of hepatitis C virus replication: the discovery of R1479. *Bioorg Med Chem Lett* 2007;**17**:2570–6.
113. Smith DB, Kalayanov G, Sund C, Winqvist A, Maltseva T, Leveque VJ, et al. The design, synthesis, and antiviral activity of monofluoro and difluoro analogues of 4′-azidocytidine against hepatitis C virus replication: the discovery of 4′-azido-2′-deoxy-2′-fluorocytidine and 4′-azido-2′-dideoxy-2′,2′-difluorocytidine. *J Med Chem* 2009;**52**:2971–8.
114. Klumpp K, Kalayanov G, Ma H, Le Pogam S, Leveque V, Jiang WR, et al. 2′-Deoxy-4′-azido nucleoside analogs are highly potent inhibitors of hepatitis C virus replication despite the lack of 2′alpha-hydroxyl groups. *J Biol Chem* 2008;**283**:2167–75.
115. Wang RR, Yang QH, Luo RH, Peng YM, Dai SX, Zhang XJ, et al. Azvudine, a novel nucleoside reverse transcriptase inhibitor showed good drug combination features and better inhibition on drug-resistant strains than lamivudine *in vitro*. *PLoS One* 2014;**9**:e105617.
116. Zhou Y, Zhang Y, Yang X, Zhao J, Zheng L, Sun C, et al. Novel nucleoside analogue FNC is effective against both wild-type and lamivudine-resistant HBV clinical isolates. *Antivir Ther* 2012;**17**:1593–9.
117. Ren Z, Luo H, Yu Z, Song J, Liang L, Wang L, et al. A randomized, open-label, controlled clinical trial of azvudine tablets in the treatment of mild and common COVID-19, a pilot study. *Adv Sci* 2020;**7**:2001435.
118. Xu N, Yang J, Zheng B, Zhang Y, Cao Y, Huan C, et al. The pyrimidine analog FNC potently inhibits the replication of multiple enteroviruses. *J Virol* 2020;**94**:e00204–20.
119. Sun L, Peng Y, Yu W, Zhang Y, Liang L, Song C, et al. Mechanistic insight into antiretroviral potency of 2′-Deoxy-2′-beta-fluoro-4′-azidocytidine (FNC) with a long-lasting effect on HIV-1 prevention. *J Med Chem* 2020;**63**:8554–66.
120. Liu Y, Liu B, Zhang Y, Peng Y, Huang C, Wang N, et al. Intestinal absorption mechanisms of 2′-deoxy-2′-beta-fluoro-4′-azidocytidine, a cytidine analog for AIDS treatment, and its interaction with P-glycoprotein, multidrug resistance-associated protein 2 and breast cancer resistance protein. *Eur J Pharmaceut Sci* 2017;**105**:150–8.
121. Peng Y, Cheng T, Dong L, Zhang Y, Chen X, Jiang J, et al. Quantification of 2′-deoxy-2′-beta-fluoro-4′-azidocytidine in rat and dog plasma using liquid chromatography-quadrupole time-of-flight and liquid chromatography-triple quadrupole mass spectrometry: application to bioavailability and pharmacokinetic studies. *J Pharmaceut Biomed Anal* 2014;**98**:379–86.
122. Ratanasuwan W, Werarak P, Koryakova A, Berzins B, Bichko V, Murphy R. Parmacokinetics of VM-1500 20 mg and 40 mg in healthy and HIV-infected patients. In: *20th international AIDS conference*; 20–25 July 2014. Melbourne, Australia. Available from: https://www.natap.org/2014/IAC/IAC_108.htm.
123. Murphy R, Kravchenko AV, Orlova-Morozova E, Nagimova F, Kozirev O, Shimonava T, et al. Elsulfavirine as compared to efavirenz in combination with TDF/FTC: 48-week study. In: *Conference on retroviruses and opportunistic infection (CROI)*; 13–16 February 2017. Seattle, USA. Available from: https://www.croiconference.org/abstract/elsulfavirine-compared-efavirenz-combination-tdfftc-48-week-study/.
124. Murphy R, Kravchenko A, Orlova-Morozova E, Nagimova F, Kozirev O, Shimonova T, et al. Elsulfavirine-based antiretroviral treatment in combination with two NRTIs: 96 weeks. In: *22nd international AIDS conference*; 23–27 July 2018. Amsterdam, Netherlands. Available from: http://programme.aids2018.org/Abstract/Abstract/7018.
125. Kang D, Feng D, Ginex T, Zou J, Wei F, Zhao T, et al. Exploring the hydrophobic channel of NNIBP leads to the discovery of novel piperidine-substituted thiophene[3,2-*d*]pyrimidine derivatives as potent HIV-1 NNRTIs. *Acta Pharm Sin B* 2020;**10**:878–94.
126. Jin K, Liu M, Zhuang C, De Clercq E, Pannecouque C, Meng G, et al. Improving the positional adaptability: structure-based design of biphenyl-substituted diaryltriazines as novel non-nucleoside HIV-1 reverse transcriptase inhibitors. *Acta Pharm Sin B* 2020;**10**:344–57.
127. Zhao C, Weber S, Schols D, Balzarini J, Meier C. Prodrugs of gamma-alkyl-modified nucleoside triphosphates: improved inhibition of HIV reverse transcriptase. *Angew Chem Int Ed Engl* 2020;**59**:22063–71.
128. Ding L, Pannecouque C, De Clercq E, Zhuang C, Chen F. Improving druggability of novel diarylpyrimidine NNRTIs by a fragment-based replacement strategy: from biphenyl-DAPYs to heteroaromatic-biphenyl-DAPYs. *J Med Chem* 2021;**64**:10297–311.
129. Boyd MA, Cooper DA. Novel antiretroviral agents and universal access to HIV care. *Lancet HIV* 2016;**3**:e2–3.
130. Kawamoto A, Kodama E, Sarafianos SG, Sakagami Y, Kohgo S, Kitano K, et al. 2′-Deoxy-4′-*C*-ethynyl-2-halo-adenosines active against drug-resistant human immunodeficiency virus type 1 variants. *Int J Biochem Cell Biol* 2008;**40**:2410–20.
131. Njenda DT, Aralaguppe SG, Singh K, Rao R, Sönnerborg A, Sarafianos SG, et al. Antiretroviral potency of 4′-ethnyl-2′-fluoro-2′-deoxyadenosine, tenofovir alafenamide and second-generation NNRTIs across diverse HIV-1 subtypes. *J Antimicrob Chemother* 2018;**73**:2721–8.
132. Murphey-Corb M, Rajakumar P, Michael H, Nyaundi J, Didier PJ, Reeve AB, et al. Response of simian immunodeficiency virus to the novel nucleoside reverse transcriptase inhibitor 4′-ethynyl-2-fluoro-2′-deoxyadenosine *in vitro* and *in vivo*. *Antimicrob Agents Chemother* 2012;**56**:4707–12.
133. Wu VH, Smith RA, Masoum S, Raugi DN, Ba S, Seydi M, et al. MK-8591 (4′-ethynyl-2-fluoro-2′-deoxyadenosine) exhibits potent activity against HIV-2 isolates and drug-resistant HIV-2 mutants in culture. *Antimicrob Agents Chemother* 2017;**61**:e00744-17.
134. Michailidis E, Huber AD, Ryan EM, Ong YT, Leslie MD, Matzek KB, et al. 4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EFdA) inhibits HIV-1 reverse transcriptase with multiple mechanisms. *J Biol Chem* 2014;**289**:24533–48.
135. Huffman MA, Fryszkowska A, Alvizo O, Borra-Garske M, Campos KR, Canada KA, et al. Design of an *in vitro* biocatalytic cascade for the manufacture of islatravir. *Science* 2019;**366**:1255–9.

136. Nakata H, Amano M, Koh Y, Kodama E, Yang G, Bailey CM, et al. Activity against human immunodeficiency virus type 1, intracellular metabolism, and effects on human DNA polymerases of 4′-ethynyl-2-fluoro-2′-deoxyadenosine. *Antimicrob Agents Chemother* 2007;**51**:2701−8.
137. Hachiya A, Reeve AB, Marchand B, Michailidis E, Ong YT, Kirby KA, et al. Evaluation of combinations of 4′-ethynyl-2-fluoro-2′-deoxyadenosine with clinically used antiretroviral drugs. *Antimicrob Agents Chemother* 2013;**57**:4554−8.
138. Stoddart CA, Galkina SA, Joshi P, Kosikova G, Moreno ME, Rivera JM, et al. Oral administration of the nucleoside EFdA (4′-ethynyl-2-fluoro-2′-deoxyadenosine) provides rapid suppression of HIV viremia in humanized mice and favorable pharmacokinetic properties in mice and the rhesus macaque. *Antimicrob Agents Chemother* 2015;**59**:4190−8.
139. Markowitz M, Gettie A, St Bernard L, Andrews CD, Mohri H, Horowitz A, et al. Once-weekly oral dosing of MK-8591 protects male rhesus macaques from intrarectal challenge with SHIV109CP3. *J Infect Dis* 2020;**221**:1398−406.
140. Barrett SE, Teller RS, Forster SP, Li L, Mackey MA, Skomski D, et al. Extended-duration MK-8591-eluting implant as a candidate for HIV treatment and prevention. *Antimicrob Agents Chemother* 2018;**62**:e01058-18.
141. Schurmann D, Rudd DJ, Zhang S, De Lepeleire I, Robberechts M, Friedman E, et al. Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration to treatment-naive adults infected with HIV-1: an open-label, phase 1b, consecutive-panel trial. *Lancet HIV* 2020;**7**:e164−72.
142. Matthews RP, Hsieh SJ, Nussbaum JC, Jajamovich GH, Zhao T, Selverian D, et al. MK-8504 and MK-8583 (tenofovir prodrugs) single-dose PK and antiviral activity in HIV infection. In: *Conference on retroviruses and opportunistic infection (CROI) 2020*; 8–11 March 2020. Boston, USA. Available from: https://www.croiconference.org/abstract/mk-8504-and-mk-8583-tenofovir-pro-drugs-single-dose-pk-and-antiviral-activity-in-hiv/.
143. Gillespie G, Rudd DJ, Zhang S, Schaeffer A, Tomek C, Larson P, et al. Fluoride pharmacokinetics in urine and plasma following multiple doses of MK-8507, an investigational, oral, once-weekly non-nucleoside reverse transcriptase inhibitor. *J Clin Pharmacol* 2022;**62**:199−205.
144. Ankrom W, Jackson Rudd D, Schaeffer A, Panebianco D, Friedman EJ, Tomek C, et al. Pharmacokinetic and safety profile of the novel HIV non-nucleoside reverse transcriptase inhibitor MK-8507 in adults without HIV. *Antimicrob Agents Chemother* 2021;**65**:e0093521.
145. Schürmann D, Rudd DJ, Schaeffer A, De Lepeleire I, Friedman EJ, Robberechts M, et al. Single oral doses of MK-8507, a novel non-nucleoside reverse transcriptase inhibitor, suppress HIV-1 RNA for a week. *J Acquir Immune Defic Syndr* 2022;**89**:191−8.
146. Buckheit Jr RW, Hartman TL, Watson KM, Chung SG, Cho EH. Comparative evaluation of the inhibitory activities of a series of pyrimidinedione congeners that inhibit human immunodeficiency virus types 1 and 2. *Antimicrob Agents Chemother* 2008;**52**:225−36.
147. Ham AS, Nugent ST, Peters JJ, Katz DF, Shelter CM, Dezzutti CS, et al. The rational design and development of a dual chamber vaginal/rectal microbicide gel formulation for HIV prevention. *Antivir Res* 2015;**120**:153−64.
148. Mahalingam A, Simmons AP, Ugaonkar SR, Watson KM, Dezzutti CS, Rohan LC, et al. Vaginal microbicide gel for delivery of IQP-0528, a pyrimidinedione analog with a dual mechanism of action against HIV-1. *Antimicrob Agents Chemother* 2011;**55**:1650−60.
149. Al-Khouja A, Shieh E, Fuchs EJ, Marzinke MA, Bakshi RP, Hummert P, et al. Examining the Safety, Pharmacokinetics, and pharmacodynamics of a rectally administered IQP-0528 gel for HIV pre-exposure prophylaxis: a first-in-human study. *AIDS Res Hum Retrovir* 2021;**37**:444−52.
150. Singer R, Derby N, Rodriguez A, Kizima L, Kenney J, Aravantinou M, et al. The nonnucleoside reverse transcriptase inhibitor MIV-150 in carrageenan gel prevents rectal transmission of simian/human immunodeficiency virus infection in macaques. *J Virol* 2011;**85**:5504−12.
151. Ugaonkar SR, Wesenberg A, Wilk J, Seidor S, Mizenina O, Kizima L, et al. A novel intravaginal ring to prevent HIV-1, HSV-2, HPV, and unintended pregnancy. *J Contr Release* 2015;**213**:57−68.
152. Friedland BA, Hoesley CJ, Plagianos M, Hoskin E, Zhang S, Teleshova N, et al. First-in-human trial of MIV-150 and zinc acetate coformulated in a carrageenan gel: safety, pharmacokinetics, acceptability, adherence, and pharmacodynamics. *J Acquir Immune Defic Syndr* 2016;**73**:489−96.
153. Li G, De Clercq E. A medicinal chemist who reshaped the antiviral drug industry: John Charles Martin (1951−2021). *Med Res Rev* 2022;**42**:647−53.
154. De Clercq E. Tenofovir alafenamide (TAF) as the successor of tenofovir disoproxil fumarate (TDF). *Biochem Pharmacol* 2016;**119**:1−7.
155. Rhee SY, Kassaye SG, Barrow G, Sundaramurthi JC, Jordan MR, Shafer RW. HIV-1 transmitted drug resistance surveillance: shifting trends in study design and prevalence estimates. *J Int AIDS Soc* 2020;**23**:e25611.
156. Siedner MJ, Moorhouse MA, Simmons B, de Oliveira T, Lessells R, Giandhari J, et al. Reduced efficacy of HIV-1 integrase inhibitors in patients with drug resistance mutations in reverse transcriptase. *Nat Commun* 2020;**11**:5922.
157. Senneker T, Tseng A. An update on neuropsychiatric adverse effects with second-generation integrase inhibitors and nonnucleoside reverse transcriptase inhibitors. *Curr Opin HIV AIDS* 2021;**16**:309−20.
158. Li G, Piampongsant S, Faria NR, Voet A, Pineda-Pena AC, Khouri R, et al. An integrated map of HIV genome-wide variation from a population perspective. *Retrovirology* 2015;**12**:18.
159. Biswas A, Haldane A, Arnold E, Levy RM. Epistasis and entrenchment of drug resistance in HIV-1 subtype B. *Elife* 2019;**8**:e50524.
160. Ding L, Zhuang C, Chen F. Druggability modification strategies of the diarylpyrimidine-type non-nucleoside reverse transcriptase inhibitors. *Med Res Rev* 2021;**41**:1255−90.
161. Jin X, Piao HR, Pannecouque C, De Clercq E, Zhuang C, Chen FE. Design of the naphthyl-diarylpyrimidines as potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) *via* structure-based extension into the entrance channel. *Eur J Med Chem* 2021;**226**:113868.
162. Link JO, Rhee MS, Tse WC, Zheng J, Somoza JR, Rowe W, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. *Nature* 2020;**584**:614−8.
163. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;**67**:1560−99.
164. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;**67**:370−98.
165. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016;**10**:1−98.
166. Ambati J, Magagnoli J, Leung H, Wang SB, Andrews CA, Fu D, et al. Repurposing anti-inflammasome NRTIs for improving insulin sensitivity and reducing type 2 diabetes development. *Nat Commun* 2020;**11**:4737.
167. Fukuda S, Varshney A, Fowler BJ, Wang SB, Narendran S, Ambati K, et al. Cytoplasmic synthesis of endogenous Alu complementary DNA *via* reverse transcription and implications in age-related macular degeneration. *Proc Natl Acad Sci U S A* 2021;**118**:e2022751118.
168. Garcia-Trejo JJ, Ortega R, Zarco-Zavala M. Putative repurposing of lamivudine, a nucleoside/nucleotide analogue and antiretroviral to

improve the outcome of cancer and COVID-19 patients. *Front Oncol* 2021;**11**:664794.
169. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* 2020;**19**:149−50.
170. Li G, Liu Y, Jing X, Wang Y, Miao M, Tao L, et al. Mortality risk of COVID-19 in elderly males with comorbidities: a multi-country study. *Aging* 2020;**13**:27−60.
171. Jiang C, Wang Y, Hu M, Wen L, Wen C, Wang Y, et al. Antibody seroconversion in asymptomatic and symptomatic patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Transl Immunol* 2020;**9**:e1182.
172. Zhou Z, Zhang M, Wang Y, Zheng F, Huang Y, Huang K, et al. Clinical characteristics of older and younger patients infected with SARS-CoV-2. *Aging* 2020;**12**:11296−305.
173. Miao M, Clercq E, Li G. Genetic diversity of SARS-CoV-2 over a one-year period of the COVID-19 pandemic: a global perspective. *Biomedicines* 2021;**9**:412.
174. Chen Z, Du R, Galvan Achi JM, Rong L, Cui Q. SARS-CoV-2 cell entry and targeted antiviral development. *Acta Pharm Sin B* 2021;**11**:3879−88.
175. Baraniuk C. Where are we with drug treatments for COVID-19?. *BMJ* 2021;**373**:n1109.
176. Del Amo J, Polo R, Moreno S, Diaz A, Martinez E, Arribas JR, et al. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy: a cohort study. *Ann Intern Med* 2020;**173**:536−41.
177. Sang Y, Ding L, Zhuang C, Chen F. Design strategies for long-acting anti-HIV pharmaceuticals. *Curr Opin Pharmacol* 2020;**54**:158−65.
178. Sax PE, DeJesus E, Crofoot G, Ward D, Benson P, Dretler R, et al. Bictegravir *versus* dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. *Lancet HIV* 2017;**4**:e154−60.
179. Sax PE, Pozniak A, Montes ML, Koenig E, DeJesus E, Stellbrink HJ, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide *versus* dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet* 2017;**390**:2073−82.
180. Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, emtricitabine, and tenofovir alafenamide *versus* dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet* 2017;**390**:2063−72.
181. Molina JM, Ward D, Brar I, Mills A, Stellbrink HJ, Lopez-Cortes L, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV* 2018;**5**:e357−65.
182. Daar ES, DeJesus E, Ruane P, Crofoot G, Oguchi G, Creticos C, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2018;**5**:e347−56.
183. Kityo C, Hagins D, Koenig E, Avihingsanon A, Chetchotisakd P, Supparatpinyo K, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) in virologically suppressed HIV-1 infected women: a randomized, open-label, multicenter, active-controlled, phase 3, noninferiority trial. *J Acquir Immune Defic Syndr* 2019;**82**:321−8.
184. Sax PE, Rockstroh JK, Luetkemeyer AF, Yazdanpanah Y, Ward D, Trottier B, et al. Switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV. *Clin Infect Dis* 2020;**73**:e485−93.
185. DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, Mills A, et al. Switching from efavirenz, emtricitabine, and tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. *Lancet HIV* 2017;**4**:e205−13.
186. Orkin C, DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. *Lancet HIV* 2017;**4**:e195−204.
187. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N Engl J Med* 2019;**381**:803−15.
188. Mills A, Crofoot Jr G, McDonald C, Shalit P, Flamm JA, Gathe Jr J, et al. Tenofovir alafenamide *versus* tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr* 2015;**69**:439−45.
189. Eron JJ, Orkin C, Gallant J, Molina JM, Negredo E, Antinori A, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. *AIDS* 2018;**32**:1431−42.
190. Orkin C, Molina JM, Negredo E, Arribas JR, Gathe J, Eron JJ, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. *Lancet HIV* 2018;**5**:e23−34.
191. Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F, et al. Tenofovir alafenamide *vs*. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr* 2014;**67**:52−8.
192. Mills A, Arribas JR, Andrade-Villanueva J, DiPerri G, Van Lunzen J, Koenig E, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis* 2016;**16**:43−52.
193. Hodder S, Squires K, Kityo C, Hagins D, Avihingsanon A, Kido A, et al. Brief report: efficacy and safety of switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) in virologically suppressed women. *J Acquir Immune Defic Syndr* 2018;**78**:209−13.
194. Maggiolo F, Rizzardini G, Raffi F, Pulido F, Mateo-Garcia MG, Molina JM, et al. Bone mineral density in virologically suppressed people aged 60 years or older with HIV-1 switching from a regimen containing tenofovir disoproxil fumarate to an elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide single-tablet regimen: a multicentre, open-label, phase 3b, randomised trial. *Lancet HIV* 2019;**6**:e655−66.
195. Molina JM, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M, et al. Rilpivirine *versus* efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 2011;**378**:238−46.
196. Cohen C, Wohl D, Arribas JR, Henry K, Van Lunzen J, Bloch M, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate *vs.* efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. *AIDS* 2014;**28**:989−97.
197. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamczer D, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 2017;**390**:1499−510.
198. Orkin C, Arasteh K, Górgolas Hernández-Mora M, Pokrovsky V, Overton ET, Girard PM, et al. Long-acting cabotegravir and

rilpivirine after oral induction for HIV-1 infection. *N Engl J Med* 2020;**382**:1124−35.
199. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masia M, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med* 2020;**382**:1112−23.
200. Overton ET, Richmond G, Rizzardini G, Jaeger H, Orrell C, Nagimova F, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet* 2021;**396**:1994−2005.
201. Orkin C, Squires KE, Molina JM, Sax PE, Wong WW, Sussmann O, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial. *Clin Infect Dis* 2019;**68**:535−44.
202. Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, et al. Doravirine *versus* ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV* 2018;**5**:e211−20.
203. Johnson M, Kumar P, Molina JM, Rizzardini G, Cahn P, Bickel M, et al. Switching to doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) maintains HIV-1 virologic suppression through 48 weeks: results of the DRIVE-SHIFT trial. *J Acquir Immune Defic Syndr* 2019;**81**:463−72.