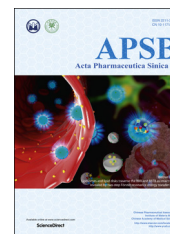




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REVIEW

Anti-retroviral drugs: current state and development in the next decade



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KEY WORDS

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Abstract The pace of discovery of new antiretroviral (ARV) drugs has slowed, although the efficacy and safety of once-daily fixed dose combinations have been extensively investigated. Several traditional ARV drugs remain in phase III clinical trials. This review summarizes current information on ARV drugs in phase III clinical trials and focuses on the development of ARV drugs in the next decade.

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1. Introduction

By the end of 2017, United States Food and Administration (US FDA) had approved 43 anti-retroviral drugs for clinical use which include 29 single-tablets and 14 fixed-dose combinations (FDCs). The intensity of the search for novel antiretroviral (ARV) compounds has slowed over the last 10 years and several traditional agents are still in phase III clinical trials. In the next decade, to improve drug safety, adherence and efficacy, the development of new anti-HIV-1 drugs will focus on long-acting formulations, oral attachment inhibitors, maturation inhibitors and new initiatives to cure the disease.

In the first decade of ARV drug therapy, these agents did not fundamentally change the destiny of those with HIV infection, although they could decrease virus load, increase CD4⁺ cell number and prolong survival over the short term. The major shortcomings were drug toxicity, drug resistance and high drug cost. Combination-based ARV therapy (ART) was introduced in 1996, which led to effectively sustained HIV suppression, significantly recovered immune function, markedly improved clinical symptoms and notably extended lifespan. In the third decade, with further development of ARV drugs and the availability of multiple ART regimens and FDCs, acquired immune deficiency syndrome (AIDS) has become a chronic, manageable and infectious disease. It is noted that in the last several years, instead of the discovery of new ARV drugs, development of effective and well-tolerated once-daily FDCs has been extensively investigated, but several traditional ARV drugs remain in phase III clinical trials. This review introduces current ARV drugs in phase III clinical trials and summarizes the development of ARV drugs over the next decade. All of the 43 FDA-approved drugs are listed here, but additional specialized reviews will be required to address new trends towards the cure of this disease.

2. Anti-retroviral drugs approved by FDA

The first AIDS cases were reported in 1981 in United States^{1,2}. The human immunodeficiency virus (HIV) was defined as etiologic microorganism in 1983^{3,4}. Just four years later, the first HIV medicine Zidovudine was approved by US FDA and quickly opened the new era for anti-retroviral chemotherapy. In the following thirty years, the FDA approved a total of 43 anti-retroviral drugs including 29 single-tablets and 14 FDCs therapeutics. These agents are classified into eight categories of ARV drugs: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors (FIs), entry inhibitors (EIs), pharmacokinetic enhancers (PEs) and fixed-dose combinations (FDCs, Table 1⁵⁻⁷).

3. Classical ARV drugs in phase III clinical trials

3.1. Tenofovir alafenamide (TAF)

TAF is a nucleotide transcriptase inhibitor (Fig. 1)^{5,8}. Tenofovir disoproxil (TDF), a new prodrug of tenofovir, has a similar structure and is in clinical use. Initially TAF was designed to improve TDF-induced renal and bone toxicity. TAF has achieved 50% effective concentrations (EC₅₀) at 11.0 and 9.7 nmol/L in CD4⁺ T cells and macrophage, respectively, and decrease of

plasma tenofovir by 90%. As compared with TDF, TAF demonstrated several important improvements. The drug can be formulated into small tablets of FDCs, has a low manufacturing cost, and shows highly reduced kidney and bone toxicity. Therefore, TAF is becoming a preferred substitute for TDF with better efficacy. Several clinical studies of TAF combinations, including elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF), rilpivirine/emtricitabine/TAF (R/F/TAF) and emtricitabine/TAF (F/TAF) were reported on November 23, 2015, March 1, 2016 and April 25, 2016.

Phase III open-label studies have evaluated the safety of E/C/F/TAF in virologically-suppressed adults with mild-to-moderate renal impairment and in treatment-naïve 12–17 year olds⁹. Whereas E/C/F/TDF is typically reserved for patients with creatinine clearance (CrCl) of at least 70 mL/min, E/C/F/TAF can be used with a pre-treatment estimated CrCl of as low as 30 mL/min⁹. Phase III randomized, double-blind clinical trials evaluating the safety and efficacy of switching to R/F/TAF in HIV-positive individuals who are virologically suppressed by either R/F/TDF or efavirenz/F/TDF (EVF/F/TDF) are under investigation¹⁰. In other phase III studies, 668 and 330 HIV-1 positive patients were recruited in F/TAF and F/TDF groups separately. Through week 48, the success cases of virological inhibition (HIV-1 RNA < 50 copies per mL) were maintained in 314 (94%) of patients in the F/TAF group compared with 307 (93%) in the F/TDF group (a difference of 1.3%, 95% CI -2.5 to 5.1), indicating the non-inferiority of F/TAF to F/TDF. Seven patients in F/TAF (2%) and three (1%) in the F/TDF group discontinued treatment due to adverse events. There were no cases of proximal tubulopathy reported in these studies¹¹.

3.2. Doravirine

Doravirine is a highly specific non-nucleoside reverse transcriptase inhibitor (Fig. 1)^{5,12,13}. The half maximal inhibitory concentrations (IC₅₀) are only 12, 9.7 and 9.7 nmol/L against the wild type HIV (WT) and 103 N and Y181C reverse transcriptase (RT) mutants, respectively. Doravirine exhibited consistent anti-HIV activities against 10 different HIV-1 subtype viruses, that the resistance suggesting that doravirine is superior overall to that *efavirenz* and comparable to that of *etravirine* (ETR) and *RPV*. A two-drug *in vitro* combination study reported that doravirine had no antagonistic actions in the antiviral activity of 18 other FDA-licensed anti-HIV drugs. *In vivo*, doravirine demonstrated robust antiviral activity and good tolerability. Data from a 48 week phase II clinical trial showed that virologic suppression (< 40 copies/mL) rates were achieved in 84% of inpatients with viral loads > 100,000 copies/mL. In addition, drug-related adverse events, including diarrhea, dizziness, and abnormal dreams, were infrequent in the doravirine group vs. the EFV group (56.5% versus 31.5%). Doravirine is currently undergoing its phase III clinical development.

3.3. Bictegravir (BIC, GS-9883)

BIC^{5,14} is a novel unboosted HIV-1 integrase strand inhibitor (Fig. 1). It inhibits HIV replication in both T-cells lines and in primary human T lymphocytes, with EC₅₀ values ranging from 1.5 to 2.4 nmol/L and selectivity indices of up to 8700. BIC demonstrates synergy of anti-HIV effects *in vitro* when combined with TAF, emtricitabine and darunavir. BIC is showing an

Table 1 US FDA approval of HIV medicines.

Year	Drug	Year	Drug
1987	Zidovudine (NRTI)	2004	Epzicom (FDC), Truvada (FDC), Cobicistat (PE), Fosamprenavir (PI)
1991	Didanosine (NRTI)	2005	Tipranavir (PI)
1992	Zalcitabine (NRTI) ^a	2006	Darunavir (PI), Atripla (FDC)
1994	Stavudine (NRTI)	2007	Maraviroc (EI)
1995	Lamivudine (NRTI), Saquinavir (PI)	2008	Raltegravir ((INSTI)
1996	Indinavir (PI), Nevirapine (NNRTI), Ritonavir (PI)	2011	Complera (FDC), Viramune XR (NNRTI), Rilpivirine (NNRTI)
1997	Combivir (FDC), Delavirdine (NNRTI), Nelfinavir (PI)	2012	Stribild (FDC)
1998	Abacavir (NRTI), Efavirenz (NNRTI)	2013	Dolutegravir (INSTI)
1999	Amprenavir (PI) ^a	2014	Cobicistat (PE), Triumeq (FDC)
2000	Didanosine EC (NRTI), Kaletra (FDC), Trizivir (FDC)	2015	Evotaz (FDC), Genvoya (FDC), Prezcobix (FDC)
2001	Tenofovir DF (NRTI)	2016	Descovy (FDC), Odefsey (FDC)
2003	Atazanavir (PI), Emtricitabine (NRTI), Enfuvirtide (FI)		

^aDrugs are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines.

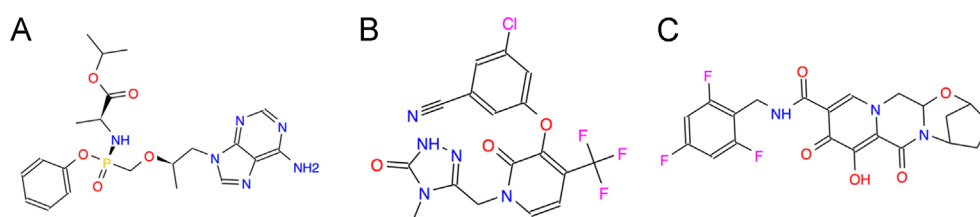


Figure 1 Classical ARV drugs in phase III clinical trials. (A) Tenofovir alafenamide (GS-7340, Vemlidy, $C_{21}H_{29}N_6O_5P$), a nucleotide reverse transcriptase inhibitor and a prodrug of tenofovir. (B) Doravirine (MK-1439, $C_{17}H_{11}ClF_3N_3O_3$), a non-nucleoside reverse transcriptase inhibitor. (C) Bictegravir (BIC, GS-9883, $C_{21}H_{18}F_3N_3O_5$), an integrase inhibitor.

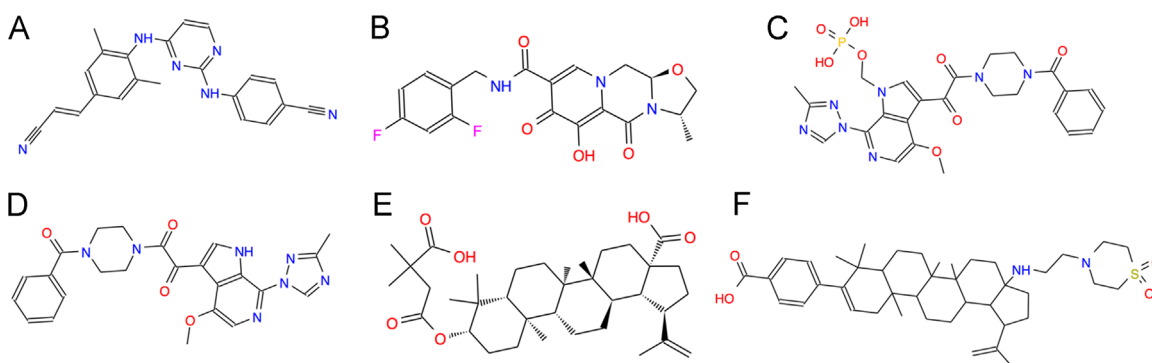


Figure 2 ARV drugs in the pipeline for the next 10 years. (A) Rilpivirine hydrochloride (Edurant; TMC278 hydrochloride, $C_{22}H_{19}ClN_6$), a second-generation NNRTI. (B) Cabotegravir (S/GSK1265744 or GSK744, $C_{19}H_{17}F_2N_3O_5$), an integrase inhibitor. (C) Fostemsavir, BMS-663068, $C_{25}H_{26}N_7O_8P$, the phosphonoxyethyl prodrug of BMS-626529, a novel small-molecule attachment inhibitor. (D) Temsavir (BMS-626529, $C_{24}H_{23}N_7O_4$), a novel small-molecule attachment inhibitor. (E) Bevirimat, BVM (MPC-4326, PA-457, $C_{36}H_{56}O_6$), the first maturation inhibitor. (F) BMS-955176 ($C_{42}H_{62}N_2O_4S$), the second generation HIV maturation inhibitor.

improved resistance profile compared to the INSTI raltegravir and elvitegravir, and was comparable to that of dolutegravir, against nine INSTI-resistant site-directed HIV-1 mutants.

Although the BIC/F/TAF combination is currently being tested in phase III clinical trials, no data from completed phase I or ongoing phase II trials has been reported. Phase III trials of BIC/F/TAF include two head-to-head comparisons with dolutegravir plus F/TAF in treat-naïve adults, with each study enrolling 600 participants in the US, Canada and other countries. Three switch phase III studies are also under evaluation, including the safety and efficacy of switching from dolutegravir plus abacavir/lamivudine (ABC/3BC) to BIC/F/TAF, a switch from boosted atazanavir or darunavir plus either F/TDF or ABC/3TC, and a switch in a cohort

comprised of HIV-positive women to all in virologically suppressed participants¹⁵.

4. ARV drugs in the pipeline for the next 10 years

4.1. Long-acting ARV formulation

Currently, ARV drugs are administered through lifelong daily oral regimens. However, poor compliance is often observed with ARVs in HIV-1 patients. When suboptimal compliance occurs, circulating ARVs are insufficient to inhibit viral replication, thereby increasing the chances of viral mutation and drug

resistance. Thus, long-acting, effective AVRs circumvent the limitations of daily oral regimens, and provide long-lasting ARV efficacy in either pre-exposure or post-exposure prophylaxis.

RPV is a second-generation NNRTI that has a longer half-life and reduced toxicity compared with previous NNRTIs (Fig. 2)¹⁶. It has been widely used as a single ARV or a combination component for HIV therapy at the oral 25 mg dose. To further extend its half-life, long-acting RPV has been investigated recently^{17–19}. Single dose administration of the long-acting RPV achieved constant drug retention in plasma for more than 6 months and 100% drug bioavailability in a pharmacokinetic study. In one phase I study of the long-acting formulation with 60 healthy HIV-negative volunteers, intramuscular or abdominal subcutaneous administered RPV was retained in the plasma for 12–26 weeks at more than 10 ng/mL. Another study of long-acting RPV reported that maximum drug concentrations of 34, 82, and 160 ng/mL at 300, 600 and 1200 mg treatment, respectively, following intramuscular administration. The half-life of this RPV formulation was more than 3 months. All of these reports indicate that the long-acting formulation of RPV is devoid of adverse drug events²⁰. More importantly, no hypersensitivity reactions or EGG abnormalities were observed. Currently, there is an ongoing phase II clinical trial for RPV.

4.1.1. Cabotegravir

Cabotegravir (Fig. 2) is an HIV-1 integrase strand transfer inhibitor. The long-acting injectable formulations of cabotegravir are being studied for clinical development^{21,22}. It is known that cabotegravir has superior ARV activity with an IC₅₀ of 0.22 and 0.34 nmol/L against HIV-1_{Bal} and HIV-1_{NL-43}. This novel integrase inhibitor specifically binds to plasma albumin protein leading to a protein-adjusted IC₉₀ of 166 ng/mL with an oral plasma half-life of 40 h. In a phase II study, once daily treatment with 5 or 30 mg cabotegravir for 10 days demonstrated excellent antiviral efficacy, with a decrease of plasma HIV-1 RNA for 2.2–2.3 log₁₀ copies/mL. Interestingly, the long-acting formulation of cabotegravir is packaged into crystal nanoparticles. Following subcutaneous or intramuscular administration, long-acting cabotegravir is slowly absorbed into blood from tissue injection sites. In a phase I trial, the long-acting injectable nanosuspension of cabotegravir were evaluated following 100–800 mg intramuscular and 100–400 mg subcutaneous injections. The therapeutically relevant plasma concentrations were achieved within 3 days after drug injection and remained in circulation from 21–50 days. Up to now, no severe injectable site reactions (ISRs), or ISR-related withdrawals have been reported for this long-acting cabotegravir formulation.

In addition, a combination of cabotegravir with RPV is being tested as a double-drug regimen for the HIV therapy²³. The phase II investigation was performed to evaluate the efficacy and safety with the oral combination of cabotegravir+RPV in HIV-1-infected

patients. At 48 week, 82% of participants across the three cabotegravir+RPV arms achieved the primary endpoint, with similar response rates across cabotegravir doses, relative to a 71% response rate in the EFV control arm. Although follow-up viral load data are not yet available, cabotegravir+RPV was generally well tolerated with no drug-related serious adverse events and few adverse event-related withdrawals.

4.1.2. Nanoformulated ART (NanoART)

NanoART is another long-acting strategy for extending the half-life of ARV drugs for HIV treatment^{24,25}. In the past ten years, nanotechnology has been employed to manipulate the formulation of the traditional ARV drug at the level of drug size, shape, and surface charge²⁶. Several studies have shown that solid crystal nanoparticles can remarkably increase drug level in blood circulation and lymphoid tissue^{27,28}. This nanoART, which selectively targets mononuclear macrophage as a cellular drug depot, delivers ARV drugs such as atazanavir to tissue reservoirs. This macrophage-mediated drug delivery facilitates long-acting drug release and achieves viral suppression for more than two weeks or even one month after single dose regimen²⁹. It was reported that the advanced nanoART, which is coated with folic acid receptors, can improve drug concentration tenfold (compared to the first generation of nanoART) in serum and lymph node over two weeks with one injection²⁸. Moreover, the novel mixed-lineage kinase 3 inhibitor (URMC-099) was observed to slow down the release of nanoART, leading to significant increases in the long-acting efficacy of nanoART^{30,31}. URMC-099 was originally discovered as an anti-neuroinflammation drug for the treatment of HIV-1 associated neurocognitive disorders (HAND) and Alzheimer's disease^{32–34}. However, the combination of anti-neuroinflammation drug URMC-099 and ARV drug nanoART has created a novel long-acting strategy for HIV eradication and further improves the cell-based drug delivery platform direct for translational application.

4.2. New attachment inhibitors

HIV-1 entry into target cells involves viral attachment, co-receptor-engagement and fusion. New attachment inhibitors which target each step of the entry process have been developed recently (Table 2). Fostemsavir (BMS-663068, Fig. 2)^{35,36} is the phosphonoxyethyl prodrug of BMS-626529 (Fig. 2), a novel small-molecule attachment inhibitor that targets HIV-1 gp120 and prevent its binding to CD4⁺ T cells. Fostemsavir inhibits HIV-1_{LAI} infection at EC₅₀ of 0.7 nmol/L. In a study of a cohort of laboratory strains, it exhibited an EC₅₀ of 0.01 nmol/L against the most susceptible HIV and an EC₅₀ value of 2 μmol/L against the least susceptible HIV. In addition, the virus was found to be resistant to other HIV entry inhibitors, such as enfuvirtide (ENF)

Table 2 Entry inhibitors that have reached late stage clinical trials.

Inhibitor	Development status	Drug class	Action against entry stage
BMS-663068	Phase III	Small molecular	Binds to region with CD4
Ibalizumab	Phase III	Post-attachment inhibitor (mAb)	Binds to CD4
Aplaviroc	Phase IIb and III	Small molecular CCR5 antagonist	Binds to CCR5
Cenicriviroc	Phase IIb and III	Small molecular CCR5 and CCR2 antagonist	Binds to CCR5 and CCR2
Sifuvirtide	Early phase	Peptides fusion inhibitor	Binds to gp41

and ibalizumab, and maintained susceptibility to BMS-626529³⁷. A phase III study of fostemsavir was initiated in February 2015.

Ibalizumab (TMB-355, also known as TNX-355) is a non-immunosuppressive monoclonal antibody that targets membrane protein CD4, the primary receptor for HIV entry. This MAb is a potent inhibitor of HIV-1 *in vitro* and shows synergy when combined with HIV gp120 antibodies or the fusion inhibitor enfuvirtide. It does not interfere with antigen presentation of immune cells^{23,38,39}. In phase I studies³⁹, intravenous injection of ibalizumab decrease the plasma HIV-1 RNA for up to 1.5 log₁₀-fold at Day 14–21 after single dose treatment. A phase II study⁴⁰ of ibalizumab reported that ibalizumab plus an optimized background regimen resulted in further decrease in plasma HIV-1 RNA compared to the background regimen alone. A subsequent phase II study also demonstrated that intravenous infusion of ibalizumab every two weeks, leading to significant viral load reduction over 24 weeks. Currently, heavily treatment-experienced patients have been enrolled in the nonrandomized arm of the phase III study to evaluate the combination treatment of fostemsavir and ibalizumab⁴¹.

4.3. The maturation inhibitors

The maturation inhibitors have been developed as a novel category of ARV drugs which targets the final step of HIV virion assembly and packaging. Unlike the PI, HIV maturation inhibitors directly bind to the HIV capsid protein and inhibit viral protein assembly into infectious HIV particle. Maturation inhibition leads to the production of noninfectious, immature virus particles. No other class of drugs shares this mechanism of action. Thus, maturation inhibitors retain inhibitory activity against HIV strains that are resistant to other classes of drugs. Several clinical trials with maturation inhibitors are underway.

Bevirimat (BVM, Fig. 2)⁴² is the first maturation inhibitor, which preferentially inhibits cleavage of SP1 from the C-terminus of HIV capsid (CA) protein. BVM has strong anti-HIV-1 IIB activity with IC₅₀ of 1.3 nmol/L. Several studies have demonstrated the following: 1. BVM induces the accumulation of the unspliced CA-SP1 intermediate in both intracellular space and virus-associated protein fractions from HIV-1-infected cells; 2. BVM has no effect on divergent sequences at the CA-SP1 junction; 3. The majority of BVM drug-resistance mutations are found on the CA-PS1 junction or within SP1.

BMS-955176 (Fig. 2)⁴³ and its backup candidate BM986173 represent second generation maturation inhibitors. BMS-955176 has a maximum reduction of viral load of 1.7 log₁₀ on a 40-mg once daily dose. This compound, unlike the first generation of maturation inhibitors, exhibits potent ARV activity against wild type HIV or HIV with baseline Gag polymorphisms. In a ten-day study of BMS-955176 monotherapy, similar antiviral activity was found in subjects with either wild type HIV or HIV with Gag polymorphisms, and in subjects with either HIV-1 subtype B or subtype C. In another study, evaluation of BMS-95166 in combination with atazanavir (with or without ritonavir boosting) showed similar maximum median declines in viral loads through Day 42. Until now, it has been found that BMS-955176 is generally well tolerated, with no adverse events requiring discontinuation. Phase II studies are under investigation including a safety and efficacy comparison with EFV (with both BMS-176 and EFV combined with TDF/FTC) and an open-label evaluation of BMS-955176 combined with dolutegravir and atazanavir in

treatment-experienced adults. Pharmacokinetics and additional safety trials are also ongoing.

5. Conclusions

In the last ten years, ART research has switched from a focus on new drug development to optimization of current fixed dose combinations⁴⁴. To approach the 90-90-90 goals of World Health Organization (WHO) by 2020 (90% of HIV-1 infected people diagnosed; 90% of those who are diagnosed started on ART; 90% of those on ART virally suppressed), current FDCs are still considered as the major therapeutic agents to fight against HIV infection. Thus, the development of long-acting formulations, oral attachment inhibitors and maturation inhibitors is urgently needed and essential for improvement of HIV therapy in the coming decade.

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References

- Centers for Disease Control and Prevention. Pneumocystis pneumonia—Los Angeles. *Mmwr Morb Mortal Wkly Rep* 1981;**30**:250–2.
- Centers for Disease Control. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men—New York City and California. *MMWR Morb Mortal Wkly Rep* 1981;**30**:305–8.
- Klatzmann D, Barre-Sinoussi F, Nugeyre MT, Danquet C, Vilmer E, Griscelli C, et al. Selective tropism of Lymphadenopathy Associated Virus (LAV) for helper-inducer T lymphocytes. *Science* 1984;**225**:59–63.
- Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* 1984;**224**:500–3.
- Horn T, Collins S. *The antiretroviral pipeline*. New York: TAG; 2016.
- Kiyota T, Morrison CM, Tu G, Dyavarshetty B, Weir RA, Zhang G, et al. Presenilin-1 familial Alzheimer's disease mutation alters hippocampal neurogenesis and memory function in CCL2 null mice. *Brain Behav Immun* 2015;**49**:311–21.
- AIDSinfo Fact Sheet. FDA-Approved Hiv Medicines. 2017. Available from: <https://aidsinfo.nih.gov/understanding-hiv-aids/infographics/25/fda-approval-of-hiv-medicines>.
- Gallant JE, Daar ES, Raffi F, Brinson C, Ruane P, DeJesus E, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV* 2016;**3**:e158–65.
- 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.
- Clinical Trials. Gov. Study to evaluate switching from a regimen consisting of efavirenz/emtricitabine/tenofovir disoproxil fumarate (EfV/FTC/TDF) Fixed Dose Combination (FDC) to emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF) FDC in virologically-suppressed, HIV-1 infected adults. [Updated 11.12.17]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02345226>.
- 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.

12. Lai MT, Feng M, Falgout JP, Tawa P, Witmer M, DiStefano D, et al. *In vitro* characterization of MK-1439, a novel HIV-1 nonnucleoside reverse transcriptase inhibitor. *Antimicrob Agents Chemother* 2014;**58**:1652–63.
13. Morales-Ramirez J.O., Gatell J.M., Hagins D.P., Thompson M., Arastéh K., Hoffmann C., et al. Safety and antiviral effect of MK-1439, A novel NNRTI (+FTC/TDF) in ART-naive HIV-infected patients. In: Proceedings of Conference on Retroviruses and Opportunistic Infections (CROI); Mar 3-6; Boston, Massachusetts: CROI, 2014.
14. Tsiang M, Jones GS, Goldsmith J, Mulato A, Hansen D, Kan E, et al. Antiviral activity of bicitgravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile. *Antimicrob Agents Chemother* 2016;**60**:7086–97.
15. Clinical Trials. Gov. Safety and efficacy of switching to A FDC of B/F/TAF from E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in virologically suppressed HIV-1 infected women. [Updated 06.11.17]. Available from: (<https://www.clinicaltrials.gov/ct2/show/NCT02652624>).
16. 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.
17. Baert L, VanT Klooster G, Dries W, François M, Wouters A, Basstanie E, et al. Development of a long-acting injectable formulation with nanoparticles of rilpivirine (TMC278) for HIV treatment. *Eur J Pharm Biopharm* 2009;**72**:502–8.
18. Verloes R, Deleu S, Niemeijer N, Crauwels H, Meyvisch P, Williams P. Safety, tolerability and pharmacokinetics of rilpivirine following administration of a long-acting formulation in healthy volunteers. *HIV Med* 2015;**16**:477–84.
19. Jackson AG, Else LJ, Mesquita PM, Egan D, Back DJ, Karolia Z, et al. A compartmental pharmacokinetic evaluation of long-acting rilpivirine in HIV-negative volunteers for pre-exposure prophylaxis. *Clin Pharmacol Ther* 2014;**96**:314–23.
20. Clinical Trials. Gov. Switch Study to evaluate the safety and efficacy of emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF) fixed dose combination (FDC) in HIV-1 positive adults who are virologically suppressed on emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF). [Updated 08.12.17]. Available from: (<https://clinicaltrials.gov/ct2/show/NCT02345252>).
21. Margolis DA, Boffito M. Long-acting antiviral agents for HIV treatment. *Curr Opin HIV AIDS* 2015;**10**:246–52.
22. Margolis DA, Brinson CC, Smith GH, de Vente J, Hagins DP, Eron JJ, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. *Lancet Infect Dis* 2015;**15**:1145–55.
23. Henrich TJ, Kuritzkes DR. HIV-1 entry inhibitors: recent development and clinical use. *Curr Opin Virol* 2013;**3**:51–7.
24. Gendelman HE, Balogh LP, Bawa R, Bradbury M, Chang EH, Chiu W, et al. Proceedings of the 4th annual meeting of the American society for nanomedicine. *J Neuroimmune Pharm* 2014; **9 Suppl 1**:S1–S3.
25. Gorantla S, Zhang G, Dash PK, et al. Nanomedicines and antiretroviral therapy. *J Neuroimmune Pharm* 2014;**9**:21–2.
26. Nowacek A, Zhang G, McMillan J, Kiyota T. Nanomedicine and neurodegenerative disorders. In: Preedy VR, Hunter RJ, editors. *Nanomedicine in health and disease*. Boca Raton: CRC Press; 2011. p. 377.
27. Li T, Gendelman HE, Zhang G, Puligujja P, McMillan JM, Bronich TK, et al. Magnetic resonance imaging of folic acid-coated magnetite nanoparticles reflects tissue biodistribution of long-acting antiretroviral therapy. *Int J Nanomed* 2015;**10**:3779–90.
28. Puligujja P, Balkundi SS, Kendrick LM, Baldrige HM, Hilaire JR, Bade AN, et al. Pharmacodynamics of long-acting folic acid-receptor targeted ritonavir-boosted atazanavir nanoformulations. *Biomaterials* 2015;**41**:141–50.
29. Guo D, Zhang G, Wysocki TA, Wysocki BI, Gelbard HA, Liu XM, et al. Endosomal trafficking of nanoformulated antiretroviral therapy facilitates drug particle carriage and HIV clearance. *J Virol* 2014;**88**:9504–13.
30. Zhang G, Dash PK, Wiederin JL, et al. Urmc-099: a mixed-lineage kinase-3 (MLK3) inhibitor with the potential to eradicate human immunodeficiency virus infection. *J Neuroimmune Pharm* 2013;**8**:437.
31. Zhang G, Guo D, Dash PK, Araújo M, Wiederin JL, Haverland NA, et al. The mixed lineage kinase-3 inhibitor URM-099 improves therapeutic outcomes for long-acting antiretroviral therapy. *Nanomedicine* 2016;**12**:109–22.
32. Dong W, Embury CM, Lu Y, Whitmire SM, Dyavarshetty B, Gelbard HA, et al. The mixed-lineage kinase 3 inhibitor URM-099 facilitates microglial amyloid- β degradation. *J Neuroinflammation* 2016;**13**:184.
33. Yang J, Hu D, Xia J, Liu J, Zhang G, Gendelman HE, et al. Enhancement of NMDA receptor-mediated excitatory postsynaptic currents by gp120-treated macrophages: implications for HIV-1-associated neuropathology. *J Neuroimmune Pharmacol* 2013;**8**:921–33.
34. Kiyota T, Gendelman HE, Weir RA, Higgins EE, Zhang G, Jain M. CCL2 affects β -amyloidosis and progressive neurocognitive dysfunction in a mouse model of Alzheimer's disease. *Neurobiol Aging* 2013;**34**:1060–8.
35. Nowicka-Sans B, Gong YF, McAuliffe B, Dicker I, Ho HT, Zhou N, et al. *In vitro* antiviral characteristics of HIV-1 attachment inhibitor BMS-626529, the active component of the prodrug BMS-663068. *Antimicrob Agents Chemother* 2012;**56**:3498–507.
36. Nettles RE, Schürmann D, Zhu L, Stonier M, Huang SP, Chang I, et al. Pharmacodynamics, safety, and pharmacokinetics of BMS-663068, an oral HIV-1 attachment inhibitor in HIV-1-infected subjects. *J Infect Dis* 2012;**206**:1002–11.
37. Li Z, Zhou N, Sun Y, Ray N, Lataillade M, Hanna GJ, et al. Activity of the HIV-1 attachment inhibitor BMS-626529, the active component of the prodrug BMS-663068, against CD4-independent viruses and HIV-1 envelopes resistant to other entry inhibitors. *Antimicrob Agents Chemother* 2013;**57**:4172–80.
38. Zhang XQ, Sorensen M, Fung M, Schooley RT. Synergistic *in vitro* antiretroviral activity of a humanized monoclonal Anti-CD4 antibody (TNX-355) and enfuvirtide (T-20). *Antimicrob Agents Chemother* 2006;**50**:2231–3.
39. Kuritzkes DR, Jacobson J, Powderly WG, Godofsky E, DeJesus E, Haas F, et al. Antiretroviral activity of the Anti-CD4 monoclonal antibody TNX-355 in patients infected with HIV type 1. *J Infect Dis* 2004;**189**:286–91.
40. Clinical Trials. Gov. Ibalizumab plus optimized background regimen in patient with multi-drug resistant HIV. [Updated 2017 Feb 8]. Available from: (<https://clinicaltrials.gov/ct2/show/NCT02475629>).
41. Jacobson JM, Kuritzkes DR, Godofsky E, DeJesus E, Larson JA, Weinheimer SP, et al. Safety, pharmacokinetics, and antiretroviral activity of multiple doses of ibalizumab (formerly TNX-355), an Anti-CD4 monoclonal antibody, in human immunodeficiency virus type 1-infected adults. *Antimicrob Agents Chemother* 2009;**53**:450–7.
42. Martin DE, Salzwedel K, Allaway GP. Bevirimat: a novel maturation inhibitor for the treatment of HIV-1 infection. *Antivir Chem Chemother* 2008;**19**:107–13.
43. Regueiro-Ren A, Liu Z, Chen Y, Sin N, Sit SY, Swidorski JJ, et al. Discovery of BMS-955176, a second generation HIV-1 maturation inhibitor with broad spectrum antiviral activity. *ACS Med Chem Lett* 2016;**7**:568–72.
44. Hedrich WD, Hassan HE, Wang HB. Insights into CYP2B6-mediated drug–drug interactions. *Acta Pharm Sin B* 2016;**5**:413–25.