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Investigational reverse transcriptase inhibitors for the treatment of HIV

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Abstract

Introduction—While considerable advances have been made in the development of antiretroviral agents, there is still work to be done. Reverse transcriptase inhibitors are important drugs for the treatment of HIV, and considerable research is currently ongoing to develop new agents and to modify currently existing agents.

Areas covered—Herein, the authors discuss both investigational nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), including agents that are in various stages of development. They also discuss novel formulations that are being investigated for currently available drugs, and discuss the advantages that these new formulations may provide.

Expert opinion—New formulations and co-formulations of currently existing antiretrovirals will represent an important area of development, as a means to improve adherence for HIV-positive individuals. New formulations will continue to be developed, with a focus on allowing for less-frequent administration, as well increasing drug concentrations at local sites such as vaginal tissue, rectal tissue and sites in the immune system.

Keywords

antiretrovirals; human immunodeficiency virus; investigational drugs; non-nucleoside reverse transcriptase inhibitors; nucleoside reverse transcriptase inhibitors

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Declaration of interest

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1. Introduction

Reverse transcriptase (RT) inhibitors, consisting of nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs), represent an important group of drugs in the treatment of HIV. Current guidelines for first-line therapy for newly diagnosed individuals with HIV recommend treatment with two NRTIs (commonly referred to as the backbone), and either a NNRTI, a boosted protease inhibitor or an integrase strand transfer inhibitor [1]. Importantly, one of the first-line recommended regimens, consisting of the NNRTI efavirenz (EFV), co-formulated with an NRTI backbone consisting of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), is commonly used in HIV therapy, as it can be given once daily, and is available as a single tablet, Atripla [1]. Other NRTI backbones are also considered first line, and there are many other NNRTIs which are used in the treatment of HIV [1].

Despite the remarkable successes of current therapies, the development of new agents is still of considerable importance. Antiviral drug resistance is a valid concern in long-term treatment regimens due to continuous viral replication and prolonged exposure to the drugs. When antiretroviral drug concentrations fall below the concentration necessary to inhibit viral replication, there is the potential for viral mutations that lead to selection of resistant strains, resulting in a loss of efficacy for that antiretroviral [2].

Additionally, new antiretrovirals are under development to attempt to improve the pharmaceutical properties of the drugs. This can include better dosing profiles, minimizing side effect profiles and increasing efficacy. Furthermore, there is considerable effort toward developing alternative dosing forms for multiple purposes, including injectable extended-release drugs, as well as vaginal and rectal gels for pre-exposure prophylaxis (PrEP). These new formulations are all efforts to improve the functionality of currently approved drugs and represent an important area in antiretroviral development [3-5].

In this review, we will focus on three different avenues in antiretroviral drug development. First, we will focus on NRTIs which are in preclinical and early clinical trials, including fentinavir, CMX-157 and tenofovir alafenamide (TAF). Next, we will discuss NNRTIs which are currently under development, including doravirine, KM-023 and a number of other novel drugs. Third, we will discuss a number of new formulations for current drugs and describe the pharmaceutical issues that these new formulations are attempting to overcome. Finally, we will provide our expert opinion on important developments of RT inhibitors for HIV.

2. Nucleoside reverse transcriptase inhibitors

The NRTI class of drugs has been the 'backbone' of antiretroviral therapy (ART) regimens for the past two decades [6]. It selectively targets the HIV-1 RT enzyme and inhibits the replication of viral RNA. These drugs do not go through Phase I metabolism in the liver and therefore are devoid of drug-drug interactions [7,8]. However, lack of Phase I metabolism also poses challenge as a result of consistent exposure of high levels of these drugs, as well as their intracellularly activated metabolites, causing toxicity [9,10]. For example, zidovudine and stavudine (d4T) cause mitochondrial toxicity. Therefore, there is a need to

develop novel NRTI agents that are safer than the existing ones and are expected to replace the existing NRTI agents [11]. The NRTIs that we will cover in this review are outlined in Figure 1.

2.1 Festinavir (BMS-986001)

Festinavir, previously known as OBM-601, is a structural analog of thymidine and is similar to stavudine (d4T) [11,12]. *In vitro* studies suggest that BMS-988001 is a weak inhibitor of host DNA synthesis and is unlikely to affect mitochondrial function. The safety profile of festinavir suggests that it is unlikely to be associated with toxicity [11]. The data from the Phase I/II study in treatment-experienced patients shows that following 10 days of monotherapy median reductions in viral load is significantly higher than the placebo at 100 – 600 mg dose [13]. Furthermore, viral susceptibility to festinavir, including the Q151M NRTI multidrug-resistant mutation, has also been studied [14]. The results show that the antiviral activity of festinavir is reduced (5- to 10-fold) in the presence of most viruses carrying M41L and D67N resistance mutations, together with K103N in the absence or presence of M184V mutation. However, viruses carrying the Q151M mutation are mildly hypersusceptible to festinavir even in the presence of K65R mutation. An additional study comprising 48-week Phase II dose-finding study in the presence of EFV and lamivudine 3TC to a control (EFV, tenofovir [TFV] and 3TC) is underway.

2.2 CMX-157

CMX-157 is a lipid acyclic nucleoside phosphonate (hexadecyloxypropyl) conjugate of TFV that delivers high intracellular concentrations of TFV diphosphate (TFV-DP) [11,15]. Its structural characteristic results in decreased circulating levels of TFV that lowers its systemic exposure and reduces the potential for renal side effects. Further, *in vitro* study has shown that CMX-157 is > 200-fold more potent than TFV. The Phase I clinical study of CMX-157 (25 – 400 mg dose) shows favorable safety, tolerability and drug profile compared with TDF. CMX157 shows a dose-dependent linear increase in appropriate plasma concentrations, and the pharmacologically active compound, TFV-DP, remains detectable in peripheral blood mononuclear cell (PBMC) after a single 400 mg dose of CMX157 for 6 days. This suggests the possibility of using CMX157 in once-weekly dosing regimen, which is further strengthened by the fact that the drug is not toxic when present in the plasma for 7 days.

2.3 TAF (GS-7340)

TAF, formerly GS-7340, is a novel prodrug of TFV. It has greater antiviral activity and better distribution into lymphoid tissues than that of the parent agent TFV [11,16]. This may translate into greater antiviral efficacy, a higher barrier to resistance and an improved safety profile relative to TDF. An *in vitro* study has shown that compared with TDF, TAF is more potent and has higher PBMC intracellular levels and lower plasma TFV exposures at ~ 1/10th of the dose [17]. More recent results indicates antiretroviral potency of TAF in relevant target cells of HIV-1 infection across multiple donors of variable gender, age and ethnicity [18]. The Phase I and Phase II clinical trials of TAF in elvitegravir/cobicistat/FTC/TAF regimen when compared with elvitegravir/cobicistat/FTC/TDF with

treatment-naïve patients show that TAF-containing regimen achieves a high rate of virological success even at relatively lower concentration than the parent [17,19,20]. In addition, patients receiving TAF-containing regimen experienced significantly smaller changes in estimated creatinine clearance, renal tubular proteinuria and bone mineral density, suggesting that it has relatively lower toxicity than the regimen containing TDF. A Phase III clinical trial evaluating a single-tablet regimen combining TAF with cobicistat, FTC and elvitegravir is underway, with extremely encouraging preliminary results [20]. There is also a plan to co-formulate the drug with cobicistat, FTC and darunavir.

3. Non-nucleoside reverse transcriptase inhibitors

NNRTIs are drugs that selectively target the HIV-1 RT enzyme. NNRTIs have been shown to interact with a non-substrate-binding site on HIV-1 RT to affect the HIV DNA polymerization step [21]. NNRTIs include delavirdine, EFV, efavirenz, nevirapine and rilpivirine (RPV). However, as observed with other classes of antiretroviral drugs, HIV-1 resistance toward NNRTI therapy and the underlying viral mutation have been reported previously [22,23]. The need for better NNRTIs has led to development of promising lead compounds and new investigational drugs. Figure 2 shows the structures of the NNRTIs that we will review in this section.

3.1 Doravirine (MK-1439)

One of the promising breakthroughs in the development of effective NNRTIs for mutant HIV-1 RT is the novel pyridone MK-1439 [24]. *In vitro* characterization revealed the wild-type HIV-1 RT inhibitory properties for MK-1439 to be comparable with existing NNRTIs. Importantly, compared to FDA-approved NNRTIs, MK-1439 was found to be active against two of the most common NNRTI-associated mutant viruses (K103N and Y181C). Moreover, initial *in vitro* screening revealed a superior selectivity (> 1000-fold) of MK-1439 in inhibiting HIV-1 RT over a panel of enzymes, receptors, transporters and ion channels.

Based on X-ray structure of the doravirine–RT complex, it was shown that the nitrogen atom in doravirine interacts with the backbone of the enzyme instead of K103 resulting in minimal impact of the viral mutation K103N on the drug's inhibitory activity [25]. Similarly, lack of interaction between Y181 and doravirine renders the mutation Y181C insignificant. Importantly, the viral mutants resistant to doravirine were found to be susceptible to NNRTIs EFV and RPV. Hence, it is rationalized that doravirine will be a suitable candidate for treating drug-naïve or NNRTI-resistant patients.

Additional advantages of this novel NNRTI include its appreciable water solubility and favorable pharmacokinetic profile [26]. In preclinical studies, conducted in rats and dogs, MK-1439 demonstrated a significantly higher systemic exposure compared to its parent lead compound. Based on a low metabolic turnover observed in human liver microsomes and hepatocytes, a once-daily, low-dose oral regimen was predicted for MK-1439.

Recent data from a 48-week efficacy and safety study for doravirine, dosed in combination with NRTIs TDF and FTC, revealed potent antiretroviral effects in HIV-1 positive ART-naïve patients [27]. In addition, compared to combination therapy including EFV,

doravirine-treated patients reported less occurrence of serious adverse effects. Furthermore, fewer patients on doravirine were reported to discontinue the treatment after 24 weeks of the study compared to EFV group.

3.2 KM-023

As part of ongoing efforts to address viral resistance toward NNRTIs, a novel compound KM-023 – (3-[3-ethyl-5-isopropyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbonyl]-5-methyl benzonitrile) – has been developed [28]. KM-023 was reported to be active against several laboratory strains and clinical HIV-1 isolated in the low nanomolar range. In addition, KM-023 showed promising antiviral activity against the EFV-resistant mutation K103N. The Phase I study assessing pharmacokinetic properties and tolerability of this drug in healthy human subjects reported no major adverse effects with this drug. Additionally, KM-023 demonstrated a dose- and time-dependent nonlinear pharmacokinetic profile, a pattern reported for first-generation NNRTIs such as nevirapine [29]. While diminished absorption due to saturation of influx transporters or enhanced clearance owing to increased metabolism are rationalized, further studies are warranted to determine the exact mechanism of nonlinear pharmacokinetics and long-term efficacy of this drug.

3.3 Lersivirine

The novel pyrazole NNRTI lersivirine, developed following structural optimization of a lead compound [30], was initially identified as a promising candidate for treating drug-resistant mutants of HIV-1 [31]. Phase I clinical trials reported a satisfactory safety and tolerability profile for the drug following 28-day daily-dosing regimen [32]. As per two separate clinical trials, lersivirine dosing had no significant impact on pharmacokinetic profiles of co-administered drugs including integrase inhibitors or protease inhibitors [33,34].

However, results from a Phase II clinical trial, conducted in comparison with another NNRTI EFV, concluded that the efficacy of lersivirine was not better than existing NNRTIs [35]. The results of the trials with lersivirine underscore the risk and difficulties associated with drug development.

4. Novel NNRTIs: promising compounds

In addition to the discussed compounds, several newly synthesized NNRTIs have displayed promising antiviral activity. For instance, a novel series of 4-substituted 1,5-diarylanilines was reported to be potent against wild-type and mutant HIV strains in nanomolar concentration range (EC_{50}) [36]. Moreover, several potent compounds from this library were found to have ideal physicochemical properties including water solubility, polar surface area, and log P value, warranting preclinical evaluation.

Efforts aimed at developing successful vaginal microbicide agent against HIV-1 have led to the discovery of a novel diaryltriazine compound, UAMC01398 [37]. In addition to high chemical stability, UAMC01398 was reported to possess excellent antiviral activity and was found to be effective against dapivirine, a microbicide drug in clinical trial, -resistant strains of HIV. Promising antiviral data for UAMC01398 prompted the development of a vaginal gel formulation for this compound [38].

Other recently reported NNRTIs include a 2,4,5-trisubstituted thiazole derivatives [39] and a novel sulfonamide compound IPK1 [40]. The thiazole derivatives inhibited RT activity at low micromolar concentrations and were effective against NNRTI-resistant strains of HIV-1. IPK1 was identified among a library of small compounds via high-throughput screening and was found to inhibit RT enzymatic activity (EC_{50}) in the micromolar concentration range. However, further structure–activity relationship studies have been proposed for the lead compounds identified from these investigations.

5. New formulations of old drugs

As new classes of antiviral drugs are not expected to come into the market in the near future, it is important to implement new strategies and new formulations using established classes to treat the HIV effectively. In recent times, significant advances have been made to simplify the ART regimen for the treatment of HIV infection. Clinical trials indicated that simplified formulations with once-daily dose show better persistent viral suppression than complex regimen through better treatment adherence [20,41,42]. These once-daily fixed-dose combinations are effective, and among recommended therapies for all HIV-infected individuals [1]. However, different components of these combination drugs may not be appropriate for all the patients due to other comorbidities and changing demographics of HIV-positive population. For example, the NNRTI EFV has been shown to be associated with psychiatric conditions [43,44]. Therefore, there is a continuing need to develop new formulations of old drugs to maintain different treatment options for the patients. This section reviews recent significant developments in the ART formulations that are at the clinical investigational stage.

5.1 Topical microbicides (vaginal and rectal gels)

Prevention of sexual HIV transmission is still a major concern in controlling HIV due to its predominant role in the spread of the disease. Surfactant and polyanion-based topical microbicides that have been tested as PrEP to block sexual transmission of HIV failed to show expected outcomes [45]. However, ART-based PrEP strategies appear promising to prevent the transmission from infected and acquisition to the uninfected individuals. The South African Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 Phase II trial showed the first positive evidence for TFV as a microbicide. In this study 1% TFV vaginal gel in a coitally associated use regimen demonstrated 39% overall effectiveness compared to placebo control [46]. In contrast, the Follow-on African Consortium for TFV Studies 001 Phase III safety and efficacy trial using same regimen as CAPRISA 004 failed to show any efficacy to prevent HIV infection which was ascribed to the poor adherence to the treatment [47]. The Vaginal and Oral Interventions to Control the Epidemic MTN 003 study that evaluated TFV tablets and vaginal gels terminated its vaginal gel arm from the study due to gel ineffectiveness in preventing HIV infection [48]. Meanwhile, the ongoing CAPRISA 008 trial is assessing the feasibility of including 1% TFV gel into existing family planning clinics [49]. Furthermore, recent studies using dapivirine, an NNRTI in vaginal gels and films demonstrated that these formulations were safe and can prevent the HIV infection with tolerable characteristics [50,51]. There are several other vaginal gel formulations with combinations of either NRTI or NNRTI at

various preclinical and clinical development stages, which were reviewed comprehensively elsewhere [52].

The successful demonstration of topical formulation of ART in CAPRISA 004 encouraged utilization of these formulations as rectal microbicides to prevent or reduce the risk of HIV acquisition through unprotected receptive anal intercourse. The Phase I rectal safety studies (RMP-02/MTN-006 and MTN-007) using CAPRISA 004 vaginal gel and slightly modified formulation revealed that the lower (5% w/w mg) glycerin formulation of TFV 1% was well tolerated and not associated with any significant mucosal damage in the rectum [53,54]. The positive safety outcomes from these trials provided a rationale to progress to a Phase II safety and acceptability study MTN-017 and the longer-term safety results are awaited.

5.2 Nanoformulations

Poor bioavailability of some of the existing ART formulations, drug resistance, lifelong daily administration and adherence challenges associated with ART regimen can potentially be mitigated by using nanoformulations. Two clinical-stage investigational long-acting nanoformulations including the second-generation NNRTI RPV (TMC278LA) and the HIV integrase strand transfer inhibitor (GSK-1265744) have been studied in Phase I trials investigating pharmacokinetic and safety. The results demonstrated that administering these agents alone or in combination are well tolerated and safe and can be used as monthly injectable regimen [55]. Likewise, a Phase IIb ongoing study is evaluating the combination oral formulation of RPV and GSK-1265744 for virological suppression maintenance (NCT01641809). These promising results are expected to support the development of long-acting injectable formulations to combat HIV infection. In addition to these clinical stage agents, receptor targeted, special encapsulation and polymer-coated formulations, which are being developed, may improve biodistribution by facilitating drug penetration into various tissue [3,56,57].

5.3 Extended release

Apart from nonadherence of treatment schedule, prevention of HIV transmission and dealing with latent virus in the viral sanctuaries of infected population are the major hurdles in ART therapy. These issues can be addressed by using formulations that can release consistent therapeutic concentration of drug, thereby preventing HIV transmission and maintaining viral suppression in the HIV-positive patients. The sustained/controlled release dosage forms that can carry the combinations of both ART and latency-breaking drugs could help achieve elimination of the virus from the system [58]. Along these lines, vaginal rings containing ART are being investigated by researchers to determine safety and effectiveness of these extended release formulation against HIV infection [52]. Safety and pharmacokinetic assessment trials for sustained release of dapivirine from vaginal rings showed that continuous and consecutive use of the product is likely protective over a month, well tolerated and safe [59,60]. Furthermore, advances in nanomedicine-based drug delivery systems have the potential to improve therapeutic options by not only sustained ART release but also by offering target-based delivery of drugs to intracellular locations/tissue like macrophages and CNS [61,62].

6. Conclusion

New NRTIs, NNRTIs and novel formulations hold considerable promise for the treatment of HIV (Table 1). Novel agents may allow for improved side-effect profiles, as well as potentially avoiding resistance to antiretrovirals that have developed over time. Additionally, there is considerable research into new formulations of both current antiretrovirals and drugs currently being investigated. These formulations may provide an exciting new way to improve adherence and increase concentrations in body areas where there are low concentrations. There is a strong pipeline of antiretrovirals in development currently, ranging from preclinical products to products that are in Phase III clinical trials, with drugs present in all stages between these phases.

7. Expert opinion

Considerable advances have been made in the treatment of HIV since the advent of modern multidrug ART. There are a few areas in which we believe that development of ART will continue to develop, and are of exceptional importance.

7.1 Improving adherence

Adherence to ART is one of the most important factors for successful therapy, and developing ways to increase adherence is an important area in antiretroviral development. This will continue to develop through a variety of methods. First, we believe that development of new antiretrovirals with pharmacokinetic profiles which support once-daily administration will continue. Once-daily administration has been shown to increase adherence. Similarly, when possible, co-formulation of antiretrovirals into a single tablet is of considerable importance. There are currently three first-line co-formulated therapeutic options which are approved for use, Atripla (TDF/FTC/EFV), Complera (FTC/RPV/TDF) and Stribild (elvitegravir/cobicistat/TDF/FTC). These therapeutic options, especially Atripla and Stribild, are used very commonly in initial HIV care, due at least in part to their ease of administration. More recently, TAF has been co-formulated with elvitegravir, cobicistat and FTC for clinical trials, and has the potential to considerably improve outcomes for HIV-positive individuals.

Co-formulation of existing products and the co-formulation of new drugs with old drugs will need to continue in the future to ensure that patients can take therapeutic modalities that are easy for them to take regularly. Further complicating this is that different pharmaceutical companies are patent holders to drugs that may make an ideal co-formulated product. Over time, as patent exclusivity is lost for existing products, this may spur the development of additional co-formulated antiretroviral products. In the face of this, there is thus considerable impetus for pharmaceutical companies to continue to develop new antiretrovirals that have better efficacy or safety profiles than currently available drugs.

7.2 Novel dosage forms

The development of extended release and topically active agents are also areas in which we believe that there will be considerable growth in antiretroviral development. Extended-release formulations, including nanomedicine-based drug delivery systems, potentially allow

for administration on a weekly basis, which would greatly change care for many individuals. A key concern to the development of these products is ensuring that these products can have shelf stability allowing for the distribution of these products through the supply chain. This is especially a concern with the developing world, where it can be difficult to ensure controlled conditions throughout the supply chain. Improving the pharmacokinetic profiles of these drugs, and other drugs can result in significant improvements in patient adherence and in outcomes for HIV-1-infected individuals who are receiving ART.

Also of considerable interest is nanoformulated ART that can be uptaken by monocytes and macrophages [4,5,62]. These are formulations that, upon administration, can be uptaken by mononuclear phagocytic cells. Once uptaken, there are two potential advantages of these products. First, the mononuclear cells release the nanoformulated drugs over time, allowing for less-frequent administration of the ART. Second, once these drugs have been internalized, mononuclear phagocytic cells can track to different locations, potentially allowing for release of ART in locations where monocytic cells track to, including lymph nodes and past the blood–brain barrier. There is also considerable research into how to increase the internalization of these products into monocytes. One approach that has been utilized is to coat the nanocrystals in folate, which has been shown to increase the extent of internalization by monocytes [4]. With continued development, this avenue of research holds considerable promise and may prove to be an exciting way to increase antiretroviral concentrations in the body, especially in areas in which low concentrations of antiretrovirals are present.

The development of topical products for PrEP is also an important issue facing drug development. Currently, PrEP with Truvada (TDF/FTC) can be extremely effective, but efficacy considerably decreases if the products are not taken. There is also considerable variation between local concentrations between vaginal and rectal sites, with vaginal concentrations being significantly lower than rectal concentrations [63]. This may limit the efficacy of oral PrEP in women. Trials using vaginal gels have shown efficacy in early trials, but larger trials have shown a lack of effect. Subgroup analyses of the CAPRISA 004 trial showed considerable differences in efficacy between individuals who were highly adherent to the therapy and those who were non-adherent to the therapy [46]. The exact cause for decreased adherence in women is unknown, but determining dosage formulations that people are willing to routinely use is an issue of considerable importance.

Additionally, the development of formulations that can penetrate into sanctuary sites, including the brain is of particular interest for the future. There has been research into embedding drugs into magnetic nanoparticles [61,64,65]. Once these products have been administered, a noninvasive magnetic field can be applied, allowing for penetration past the blood–brain barrier. Overcoming pharmacologic sanctuaries, including those in the brain, is an important issue, while viral replication can effectively be minimized in the plasma in many treatment-adherent patients, drug concentrations in sanctuary sites are subtherapeutic, which may lead to ongoing replication [2,16]. These sites can include the brain.

While outcomes for individuals with HIV have improved greatly, the development of new antiretrovirals must continue. The development of novel NRTIs and NNRTIs is an important

part of this process. Developing new agents that can be used in patients who have resistant virus is of key importance. Also important is the development of drugs that have fewer side effects than current medications. Bothersome side effects are one of the leading reasons why individuals stop taking their medications, and developing medications that minimize these side effects can additionally lead to improved outcomes.

7.3 Difficulties in developing new antiretrovirals

The development of new drugs is a process fraught with failure. As a drug progresses through the different stages of clinical trials, there is always a chance of failure, and as drugs progress into later stages of trials, failure becomes increasingly expensive. The case of lersivirine underscores the difficulties associated with the drug development process. Ideally, altering the drug development process to attempt to identify better lead compounds may decrease the amount of failures that occur in later phases of clinical trials. This may include more preclinical testing, and optimization of lead compounds to ensure a better absorption, distribution, metabolism, and excretion profile. Additionally, improving the drug development process to identify drugs that should be eliminated from the development process earlier is an issue of key importance. Identifying the drugs that would fail in later stage trials earlier has the potential to save considerable amount of money, time and effort in the drug development process. Developing approaches to 'fail earlier' with drugs in development will play an important role in minimizing the costs associated with drug development.

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Article highlights

- New nucleoside reverse transcriptase inhibitors (NRTIs) are under development that have better side-effect profiles and may be able to treat resistant virus.
- These new products include festinavir, which is chemically similar to stavudine, and tenofovir alafenamide, which is a prodrug of tenofovir, which has shown considerable promise in clinical trials.
- There are considerable promising non-nucleoside reverse transcriptase inhibitors (NNRTIs), including doravirine, which are active against two common NNRTI-associated mutant viruses.
- Considerable research has been performed assessing topical formulations of currently approved antiretrovirals primarily for pre-exposure prophylaxis.
- Nanoformulations for currently approved drugs may allow for better absorption, as well as distribution through the body to sites that have low antiretroviral concentrations.

This box summarizes key points contained in the article.

Parent compound	Novel analogs/prodrugs	Phase
<p>Stavudine</p>	<p>Festinavir (BMS-986001)</p>	II
<p>Tenofovir</p>	<p>CMX-157</p>	II/III
	<p>GS-7340 (Tenofovir alafenamide fumarate)</p>	III

Figure 1.

Schematic representations of the novel analogs/prodrugs of existing NRTIs under different clinical development phases.

NRTI: Nucleoside reverse transcriptase inhibitor.

Doravirine (MK-1439)	KM-023	Lersivirine

Phase II	Phase I	Phase II

Figure 2.

Schematic representations of the new NNRTIs under different clinical development phases.

NNRTI: Non-nucleoside reverse transcriptase inhibitor.

Table 1

Overview of major drug categories.

Category of drug	Drug	Comments
NRTIs	Festinavir	Stavudine analog Good safety profile
	CMX-157	Lipid acyclic nucleoside phosphonate conjugate of TFV More potent than TFV
	Tenofovir alafenamide	Prodrug of TFV Higher intracellular concentrations than TDF
NNRTIs	Doravirine	Good safety profile High selectivity for HIV-1 RT
	KM-023	No major issues in Phase I trial
Novel formulations	Topical microbicides	Primarily investigated for pre-exposure prophylaxis Work well in adherent subjects
	Nanoformulations	Less-frequent administration possible May allow for improved biodistribution
	Extended release	Way to prevent low level replication Vaginal rings may provide antiretrovirals for a month

NNRTI: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside reverse transcriptase inhibitor; RT: Reverse transcriptase; TDF: Tenofovir disoproxil fumarate; TFV: Tenofovir.