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Emerging Reverse Transcriptase Inhibitors for HIV-1 Infection

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Abstract

Introduction: There are 36.7 million people living with HIV with 20.9 million having access to antiretroviral therapy (ART). Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) remain the 'backbone' of ART. However, the currently available nine NRTIs and five non-nucleoside reverse transcriptase inhibitors (NNRTIs) have significant side effects and resistance profiles.

Areas covered: We summarize the mechanisms of resistance and other limitations of the existing NRTIs/NNRTIs. GS-9131, MK-8591, Elsulfavirine and Doravirine are four new agents that are furthest along in development.

Expert opinion: ART development has evolved with several new promising agents. Longer-acting agents, like MK-8591 are extremely attractive to enhance drug adherence and patient satisfaction. Doravirine offers an NNRTI effective against common mutations that has fewer side effects, limitations on dosing and drug interactions. GS-9131 is very potent and active against a variety of NRTI mutants but it is too early in its development to understand its full risks and benefits. Finally, Elsulfavirine has a long half-life and preliminary data suggests fewer side effects than the most commonly used NNRTI, efavirenz. Each of these new agents shows promise and potential to improve ART in the future. The newer generation of reverse transcriptase inhibitors have longer half-lives, more favorable adverse effect profiles, and fewer drug interactions.

Keywords

HIV Reverse Transcriptase Inhibitors; GS-9191; MK-8591; Elsulfavirine; Doravirine; NNRTI; NRTI; Nucleoside reverse transcriptase inhibitors; Non-nucleoside reverse transcriptase inhibitors; HIV

1. Background

According to the latest data from UNAIDS, 76.1 million people have become infected with HIV since the start of the epidemic, and globally, 36.7 million people globally were living with HIV in 2016 [1]. Even though the number of new infections continues to decrease, it still continues to have significant morbidity and mortality, with nearly 2 million new

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infections, and almost 1 million people dying from AIDS related illnesses in 2016 [2]. As of June 2017, 20.9 million people living with HIV were accessing antiretroviral therapy (ART), a number which has gone up from up from 17.1 million in 2015 and 7.7 million in 2010 [3]. ART has had dramatic effects on decreasing mortality from HIV with life expectancy of HIV-infected adults in both high- and low-income countries now reaching that of the general population in those who start therapy early, are adherent and have access to healthcare services [4–6]. Given the critical importance of ART in the treatment of HIV-infected persons, it remains a crucial component of UNAIDS's global aims to achieve by the year 2020. The 90–90-90 initiative aims to ensure that a high proportion (90%) of people are tested for HIV infection, receiving ART, and sustain viral suppression [7]. Yet, a significant portion of the world's population, particularly adults in Western and Central Africa, the Middle East and North Africa, have severe limitations in accessing ART (36% and 24% respectively) [1]. All of these sobering figures serve to emphasize that even though the HIV epidemic has transitioned to an endemic phase, any delay or despondency in tackling its various parameters at play risks translation into more ominous outcomes [8].

ART has had tremendous impact soon evident after its introduction in 1995 leading to massive declines in mortality and morbidity, as demonstrated in the ground-breaking HIV Outpatient Study [9], eventually transforming HIV into a chronic, usually non-fatal condition in the developed world. Reverse transcriptase inhibitors remain the central 'backbone' of antiretroviral therapy, since the first NRTI was introduced [10] (Zidovudine was the first NRTI which got approval by the FDA in 1987). There are two distinct types of reverse transcriptase inhibitors, the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). The NRTIs undergo intracellular phosphorylation, and the active triphosphate form thereafter inhibits viral replication through competition with naturally occurring purines and pyrimidines, preventing the addition of further nucleotides by reverse transcriptase (RT), and hence terminating viral DNA replication [11]. The NNRTIs bind to a hydrophobic pocket in the palm subdomain of p66, a site that is separate from the active site targeted by the NRTI class [12]. This binding of the NNRTIs leads to a stereo-chemical change in the protein, which reduces the ability of naturally occurring nucleosides to bind to the active site pocket, and hence block viral cDNA elongation [13].

There are currently nine NRTIs and five NNRTIs available. These currently require daily administration in combination with other agents to maintain viral suppression. The costs of therapy range from $400 annually in less resource rich Nations to $12,000–15,000 in resource rich Countries. The estimated costs of treating all persons living with HIV is $20 billion dollars annually [14]. The NRTIs are typically combined with a third agent (e.g., NNRTI, protease inhibitor or integrase inhibitor) for initial therapy. This remains the standard approach worldwide to therapy. The main threats affecting the use of the reverse transcriptase inhibitor classes of medications include the emergence of resistance, toxicity and intolerance of medications, and the requirement for daily administration. One theoretical advantage despite the development of resistance is impaired viral fitness. The M184V mutation to lamivudine or emitracitabine has been associated with impaired viral fitness in vivo yet there are no clinical data indicating this improves the morbidity or mortality from

HIV infection [15]. In this review, we will discuss the advantages and disadvantages of currently available reverse transcriptase inhibitors and four emerging drugs within this class.

2. Medical need and current therapeutic class review

It is testament to the immense success against HIV that 20.9 million people now have access to ART, which amounts to approximately 53% of the estimated 36.7 million people living with HIV globally [3]. AIDS related deaths have fallen by 48% to 1 million since the peak of 1.9 million in 2005 [3]. The aim of ART revolves around four major parameters: to reduce HIV-associated morbidity and prolong the duration and quality of survival; to maximally and durably suppress plasma HIV[i] RNA replication; to prevent HIV transmission; and restore and preserve immunologic function. We have come a long way but significant challenges remain [16].

The daily requirement for an ART regimen translates into patient fatigue after years of use, and it is no surprise that in a meta-analysis that synthesized eighty-four observational studies from twenty countries, it was found that fewer than 62% of patients maintain the ≥90% adherence which is required for optimal viral suppression [17]. Pre-exposure prophylaxis (PrEP), recommended by the World Health Organization (WHO) for high-risk populations with HIV incidence of ≥3%, has adherence which ranges from 28% to 98% [18]. Adherence to ART is also greatly confounded in patients who have other medical conditions including substance abuse and psychiatric disorders [19], not to mention those who must take more than a one pill per day ART regimen [20].

The other major challenge of a life-long therapy and a mutating virus is resistance to existing HIV medications [21, 22]. In this context, the existing of pretreatment resistance becomes even more daunting of a challenge in resource-limited settings, where resistance testing is not widely available. It has been recently shown in a systematic review and meta-regression analysis of 358 datasets, representing 56,044 adults in 63 countries, that pretreatment NNRTI resistance in 2016 at about 10% in most regions -- 11% in southern Africa, 10.1% in eastern Africa, 7.2% in western and central Africa, and 9.4% in Latin America and the Caribbean [23]. Currently, there are more than 25 antiretroviral medications from six major classes available for the treatment of HIV-infected patients. For the purpose of this review, we will focus on the reverse transcriptase inhibitors.

The spectrum of activity of NRTIs includes both HIV-1 and HIV-2, and they constitute the ‘backbone’ of ART (Table 1). Of the major NRTIs, Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are adenosine-derived; Emtricitabine and lamivudine are cytosine analogs; Abacavir sulfate is a guanosine analog; Zidovudine and stavudine are thymidine analogs; and Didanosine, is inosine derived. All of the NRTIs have class and drug specific side effects and can select for resistance mutations. Major side effects for TDF include kidney injury and bone loss [24–27]. TAF has less renal and bone toxicity because of the lower plasma concentrations [28], but leads to higher levels of LDL and HDL cholesterol, as well as triglycerides [29]. Lamivudine has been associated with pancreatitis [30], and Emtricitabine can cause skin hyperpigmentation [31]. The use of Abacavir in patients with high viral loads (>100,000 copies) remains a concern because of higher rates of

treatment failure, as well as its suspicion for being associated with higher rates of myocardial infarctions [32, 33]. Zidovudine requires twice daily dosing and its major dose-limiting toxicity is bone marrow suppression. In addition, zidovudine is associated with a myriad of adverse reactions including headache, malaise, anorexia, nausea, vomiting, lactic acidosis, and loss of limb fat. Didanosine and Stavudine are used rarely because of their adverse effect profile including neuropathy, lipodystrophy, and mitochondrial toxicity. The most commonly used combinations are available as co-formulations: tenofovir disoproxil fumarate-emtricitabine (Truvada®), abacavir-lamivudine (Epzicom®) and tenofovir alafenamide-emtricitabine (Descovy®) in the United States. All of the NRTIs can select for resistance mutations, and this occurs via two different mechanisms. The first involves a mutated viral reverse transcriptase enzyme (mutations in the N-terminal polymerase domain of the enzyme) that selectively avoids incorporating the nucleotide analogs into the DNA instead of the normal nucleotides. The most common mutations in this category include K65R, L74V, Q151M, and M184V [34–36]. The second mechanism involves thymidine analog mutations (TAMs) – essentially the mutated reverse transcriptase enacts the phosphorolytic excision of NRTIs from the 3′ end of the viral DNA chain that extends from the primer, a process referred to as “primer unblocking” [37, 38]. TAMs include M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E, and they confer resistance to all NRTIs except lamivudine (3TC) and emtricitabine (FTC). The NRTIS have few clinically significant drug-drug interactions because they are not substrates, inhibitors, or inducers of hepatic cytochrome P450 (CYP) enzymes. In summary, currently available NRTIs have significant side effect profiles, known problems with resistance and must be administered on a daily or twice daily basis.

The NNRTIs are active against HIV-1 but lack activity against HIV-2 (Table 2). The NNRTIs are typically administered along with a dual NRTI combination. The first generation NNRTIs includes efavirenz and nevirapine; second generation NNRTIs are rilpivirine and etravirine. The first-generation agents have a low threshold to acquire resistance and only need a single mutation. One of the major mutations, K103N leads to cross-resistance to all first generation NNRTIs. The NNRTIs have a long plasma half-life and can act as perpetrators of drug interactions. Efavirenz has multiple drug interactions and needs a thorough review of concomitantly administered drugs. In addition, it has a significant side-effect profile that includes neuropsychiatric toxicity, rash, hyperlipidemia and elevated transaminases [39, 40]. The side effect profile is worse in black patients, and long term mental health consequences including suicide have overshadowed Efavirenz’ usage [41]. Nevirapine is not recommended as an initial regimen in treatment-naïve patients [42], because of its increased toxicity that includes hepatic necrosis and serious cutaneous reactions, including deaths due Stevens-Johnson Syndrome [43, 44]. Rilpivirine can be used in treatment-naïve patients with a baseline viral load of <100,000 copies/mL and CD4 count of >200 cells/mm^3. It has been associated with QT interval prolongation, and as it needs gastric acid, requires administration with a meal and concomitant use of proton pump inhibitors is contraindicated. Rilpivirine also has important drug interactions and causes neurologic and psychiatric side effects, though fewer than efavirenz [45]. Etravirine is used primarily when there is a resistant virus, and its most common side effect is rash. It also needs adjustments because of its significant drug interactions.

Mutations conferring NNRTI resistance involve decreasing the binding of the agent to the NNRTI binding site. There are three main mechanisms: the contact of the drug could be inhibited to the NNRTI binding pocket (e.g., K103N and K101E) [46, 47]; disruption of the contact between the inhibitor and residues in the NNRTI binding domain (e.g., Y181C and Y188L) [48, 49]; or changes in the conformation or size of the NNRTI binding pocket (e.g., Y188L and G190E) [49]. Hence, the significant interactions and side-effect profiles render use of NNRTIs problematic.

3. Current research goals and scientific rationale

There is a strong scientific rationale to design of novel agents within existing classes, particularly PIs, NNRTIs and NRTIs, INSTIs with improved pharmacological properties, tolerance, and activity against drug-resistant HIV. Developing agents that are active against drug-resistance mutants is important to have sufficient options to treat those that failure standard ART. Because of the significant adverse effects of existing agents, developing safer therapy is key. Finally, because adherence to daily therapy is challenging over a lifetime, developing longer-acting agents is of paramount importance.

A major impetus to address inadequate adherence levels is the development and implementation of long-acting agents [50, 51]. The primary goal is to address the challenges of life-long drug adherence. Significant research has been focused on long-acting Cabotegravir, an integrase strand transfer inhibitor [52]; Long acting Rilpivirine, a NNRTI [53]; drug loaded inserts (Dapivirine Vaginal Ring) [54] and implants (Tenofovir Alafenamide Implant) [55]; microparticles [56]; Atazanavir with ritonavir [57]; Combinectin, BMS-986197 [58] and MK-8591 (discussed below in detail). One potentially new paradigm is combining two long-acting agents using injectable medications. This includes the NNRTI rilpivirine in combination with an integrase strand transfer inhibitor. In the randomized, phase 2b, open-label LATTE-2 study of treatment-naive adults infected with HIV-1, the two-drug combination of all-injectable, long-acting cabotegravir plus rilpivirine every 4 weeks or every 8 weeks was as effective as daily three-drug oral therapy at maintaining HIV-1 viral suppression through 96 weeks [59]. The emerging use of longer acting agents may herald a new treatment paradigm in preventing and treating HIV infection.

4. Competitive Environment

The development of new NRTIs and NNRTIs focus on improved coverage of HIV resistant mutants, fewer side effects and improvements in pharmacologic properties. The mechanism of action of new NRTIs and NNRTIs are similar to the existing ones with no major breakthrough. We review four promising agents (Table 3): GS-9131, MK 8591, Elsulfavirine and Doravirine that are most advanced in their development.

a. GS-9131

GS-9131 is a designer NRTI under development by Gilead Sciences [60]. Building upon the nucleoside phosphonate d4AP which was discontinued from further development because of mitochondrial toxicity, a 2’-fluorine substitution modification led to development of

GS-9148 and its orally bioavailable phosphonoamidate prodrug, GS-9131 [61–62]. Using the PhenoSense HIV assay to determine activity and resistance profile of GS-9131, it was shown to have potent antiretroviral activity against HIV-1 isolates of subtypes A, B, C, D, E, F, group O and N (EC_{50} 0.29–113 nM) [63]. In addition, it also potent activity against HIV-2 (EC50 = 21 nM) with low cytotoxicity in multiple cell types including renal cells (CC50 > 100 μM) [64, 65]. The presence of RT mutations K65R, L74V, M184V or their combinations did not affect the potency of GS-9131 (EC_{50} fold change < 1). GS-9131 acts in a synergistic fashion in combination studies with AZT, FTC, ABC, efavirenz, the integrase inhibitors bictegravir and dolutegravir, and the protease inhibitor, lopinavir. It has additive effects with TFV and TAF [66]. However, GS-9131 has been shown to select for the very rare Q151L mutation in HIV-1 RT as a pathway to resistance, and interference experiments have shown that Q151L severely compromises binding of GS-9148-diphosphate to RT, and the 2'-fluoro group of GS-9148 may cause steric hindrance with the side chain of the Q151L mutant [67]. GS-9131 may be an attractive candidate with a potential for once daily dosing and efficacy in patients with NRTI resistance. However, with its propensity for selecting Q151L mutation, it is possible the utility of GS-9131 will be restricted.

b. MK 8591

MK-8591 (4′-ethynyl-2-fluoro-2′-deoxyadenosine [EFdA]), an NRTI, is being developed by Merck & Co [68]. It has highly potent activity against HIV-1 and HIV-2, with very favorable toxic profiles, and stability in plasma [69–70]. This agent is 10-fold more potent than tenofovir disoproxil fumarate (TDF) [71], and 1,000 times more potent than emtricitabine (FTC) [72]. What makes MK 8591 particularly interesting is its long intracellular half-life – this is due to the fluorine at position 2 of the adenine base, which essentially confers resistance to degradation by adenosine deaminase [69, 70]. It was shown to have antiviral activity for ten days in ART-naive, HIV-1-infected participants when administered as a single 10 mg dose in a phase 1b proof-of-concept clinical trial [73]. More recent data suggests that a dose as low as 0.5 mg would suppress HIV replication for at least 7 days [74]. In healthy individuals, daily doses of 0.25 mg exceed the EC_{50} of HIV with adequate intracellular levels in plasma, rectal and vaginal tissues [75]. Also, it was shown that long-acting parenteral formulations of MK-8591 exhibited continuous, extended-duration drug release in rodents with MK-8591 plasma levels comparable to those achieved in rhesus and humans and duration of release exceeding 6 months [76]. With possible weekly dosing, this potential drug would represent a paradigm shift in treatment of infection, helping to greatly aid in patient compliance with their HAART regimen. There is ongoing research which suggests that a single dose of MK 8591 may be able to achieve effective concentrations for up to a year [76]. Data from Macaques support the potential use of MK-8591 for HIV-1 prophylaxis in individuals at high risk of acquiring infection [77]. In summary, MK 8591 can revamp the treatment administration timing for HIV infected patients, as well as have a possible role for HIV prevention. This drug can tackle many of the problems currently encountered when treating HIV patients on HAART, ranging from poor adherence to the development of drug-resistant virus.

c. Elsulfavirine / VM-1500A

The San Diego based Biotech Company Viriom is developing Elsulfavirine or VM-1500A, an NNRTI, also known by its brand name Elpida®. It is under development as a once-daily oral regimen and there are studies underway for long acting injectable preparations of VM-1500A. It was shown to be safe in a combined Phase Ib and IIa randomized, placebo-controlled, double-blind study of VM-1500 in healthy subjects and in patients with HIV-1 infection that are antiretroviral therapy naïve (Study identifier NCT02485509) [78, 79]. In healthy participants, the half-life of VM-1500A was 8.9 days (20-mg dose) and 8.8 days (40-mg dose) [78]. In the HIV infected cohort, the half-life of the VM-1500A metabolite after 7 days was 7.4 days (20-mg dose) and 5.4 days (40-mg dose) [78]. The next Phase IIb study (Study identifier NCT02489461) compared the efficacy of Elsulfavirine to Efavirenz in combination with TDF/FTC [80]. The study showed that Elsufavirine had similar virologic control to Efavirenz, with therapy 45/55 (81%) of Elpida and 35/47 (73.7%) of EFV patients had HIV-1 RNA values <50 copies/ml at week 48 [80]. More interestingly, Elsulfavirine was significantly better tolerated than EFV-based therapy, with drug-associated adverse events being observed in 36.7% (N=22/60 participants) in the Elsulfavirine group versus 77.6% (N=45/58 participants) in the EFV group ($p < 0.0001$). There were no allergic reactions or skin rash observed [80]. The Russian Ministry of Health granted approval of this drug in June 2017 as an oral 20 mg capsule but it has yet to be approved in the United States or Europe [81]. The company is currently working on developing long-acting, injectable formulations. In summary, Elsulfavirine appears to have a much better side effect profile compared to Efavirenz though data are limited at this point. If confirmed in additional studies this would aid in its applicability as a potential first line treatment regimen.

d. Doravirine

Doravirine, formerly MK-1439, is an NNRTI developed by Merck & Co. It is a designer drug fashioned to overcome resistance patterns which plague the NNRTIs. It was shown to have more than 30-fold improved potency compared to that of Efavirenz against K103N mutant virus and more than 9- and 4-fold better potency than Etravirine and Rilpivirine, respectively, against Y181C mutant virus, in the presence of 50% serum [82]. It has potent activity against a wide range of resistant mutant HIV viruses [83]. In a Phase IIb study involving ART-naïve HIV-1-positive patients also receiving TDF/FTC, Doravirine 100 mg daily showed potent antiretroviral activity at week 48. There were significantly fewer treatment-emergent central nervous system side effects by week 8 than those who received Efavirenz [84]. Doravirine reduced HIV viral load by about 1.3 logs in a 7-day monotherapy dose-escalation study [85]. Doravirine also demonstrated no significant alterations in atorvastatin pharmacokinetics in healthy subjects, lending credence to its usage with atorvastatin [86]. In addition, moderate hepatic impairment did not have any meaningful effect on doravirine pharmacokinetics indicating that no dose adjustment is required [87]. Food was also shown to have no clinically meaningful effect on doravirine 100 mg alone or as part of an fixed drug combination [88]. Recently, as a part of DRIVE-AHEAD, a Phase II trial, it was shown that a once-daily single tablet, fixed-dose combination of Doravirine (DOR), lamivudine, and tenofovir disoproxil fumarate was not inferior to a fixed-dose combination of efavirenz, emtricitabine, and TDF, in treatment-naïve adults infected with HIV-1 [89]. In addition, the incidence of dizziness, sleep disorders/disturbances, and altered

sensorium was lower in DOR/3TC/TDF recipients than in EFV/FTC/TDF recipients ($p< 0.001$, $p< 0.001$, and $p=0.033$, respectively) [89]. Interestingly, fasting LDL-C and non-HDL-C were reduced by DOR/3TC/TDF and increased by EFV/FTC/TDF (both $p< 0.0001$) [89]. Doravirine shows promise as a first-line regimen with its activity against virus with classic NNRTI mutations, including K103N, Y181C, and G190A. In addition, its limited side-effect profile, lack of requirement for food to enhance absorption, minimal drug interactions and lack of dose adjustment requirement for moderate liver disease, makes it an attractive antiretroviral agent.

5. Potential Development Issues

Three of these agents appear to be well on their way in the drug development process. GS-9131 is a derivative of nucleoside phosphonate d4AP that had significant mitochondrial toxicity. Whether the structural similarity will affect tolerability or development is unclear. Both doravirine and elsufavirine must contend with a market place that has integrase strand transfer inhibitors as the primary initial agents used in ART. Head to head trials may be required to determine the niche for these agents. Identifying the dosing interval for MK-8591 is the key issue for this agent. In addition, the developers will need to decide if they wish to concentrate on HIV prevention or treatment.

6. Conclusion

We have presented data on four potential reverse transcriptase inhibitor antiretroviral options in the pipeline. Each of these agents has unique properties that make them potentially useful in the armamentarium to prevent and treat HIV infection. Doravirine is effective in many NNRTI resistant isolates and has fewer side effects than Efavirenz. Elsulfavirine also appears to be as effective as Efavirenz with fewer side effects in preliminary studies. Both MK-8591 and GS-9131 are earlier in the development process though each has promising pharmacologic characteristics to add to the field. The most important development in the field would be the implementation of agents with longer half-lives, spanning days, if not weeks and months. This would aid greatly in patient adherence and potential reduce the development of drug resistance. Recent data has actually shown that a four or eight week maintenance ART injection of cabotegravir plus rilpivirine had high rates of virologic response and was well tolerated through 96 weeks, with very high patient satisfaction [59]. These data signify a paradigm shift in ART administration. MK 8591 has qualities that lend to development as a long-acting agent. In summary, the newer generation of reverse transcriptase inhibitors appear to have more favorable adverse effect profiles and fewer drug interactions in preliminary studies making them attractive to administer in patients with multiple co-morbidities if confirmed in future trials.

7. Expert Opinion

Antiretroviral therapy has transformed the natural history of HIV infection with reverse transcriptase inhibitors making a substantial impact on decreasing morbidity and mortality. The past thirty years has seen the development of six classes of drugs directed at the life cycle of HIV. Over the last decade, ART has become increasingly tolerable and moved to

fixed dose combinations to improve adherence. The existing paradigm includes reverse transcriptase inhibitors as a standard backbone with a third potent agent. First line ART in 2018 increasingly consists of an integrase inhibitor in combination with two NRTIs. However, NNRTIs remain an important component of first line therapy particularly in resource poor nations. The horizon will include longer-acting agents with a potential paradigm shift to intermittent administration of ART to further improve adherence. In addition, because of the side effects of NRTIs, combination therapy omitting this class of agents is emerging. Although there is data to suggest that HIV with a M184V mutation because of exposure to lamivudine or emitracitabine are less fit, there is no data to support this has a real clinical advantage. The next decade will likely continue to see shifts in treatment of HIV.

So, how can we use these new reverse transcriptase inhibitors? The two NRTIs, GS-9131 and MK-8591, must provide an advance over existing formulations. MK-8591 appears to have the most promise with a very long half-life. Clearly, there is potential as an intermittently dosed agent or provide a measure of security in those with inadequate adherence. It is attractive for both HIV prevention and treatment. However, there has not been enough human data to understand its efficacy and side effects. Furthermore, if individuals stop other agents, will the prolonged half-life and residual levels ultimately lead to the emergence of drug resistance? If there is protracted exposure to sub-therapeutic plasma concentrations, that could lead to viral resistance to not just MK 8591 but also possibly other agents in the same class. GS-9131 may be useful for treating drug resistance strains. It is valuable to have active agents from multiple classes when treating individuals with drug resistance. However, there is a long way to go in the development of this agent. The issue of whether GS-9131 has mitochondrial toxicity requires an answer before this agent comes into clinical use.

The two NNRTIs are much closer to the clinic. We need additional studies with both of these agents to see how they fit in the larger picture of ART. Integrase strand transfer inhibitors are the first choice for a potent agent to combine with NRTIs as initial therapy. Ideally, we need randomized studies to understand how these agents compare to this class of drugs. Doravirine is under development as a combination agent with TDF that has more toxicity than TAF. It seems to be unwise to proceed with development of this single fixed-dose combination given the known safety issues with TDF. Elsulfavirine has potential to be a long-acting agent. It is unclear whether there is enough of an advantage to merit much use of this agent compared to other available antiretrovirals as a first line oral agent. It is hard to imagine how Doravirine and Elsulfavirine will supplant other agents in the absence of comparisons with other first line therapies.

Finally, cost is another important consideration for all of these new agents. A cost of $40 000-$70 000 annually for long-acting ART will offer good value for patients with multiple prior failures [90]. However, to be a viable option for first- or second-line therapy, long-acting therapy costs must approach that of currently available regimens. With the recent FDA approval for ART regimen consisting of the fixed dose combination of two agents (Juluca®, a combination of dolutegravir and rilpivirine) for individuals with a suppressed viral load and on a stable regimen for at least six months, there is already a shift in the

paradigm of treating HIV away from the backbone of NRTIs. Other two drug combinations are under study. It is unknown whether we can use these new agents in dual combination regimens. NRTIs and NNRTIs remain important components of ART but newer agents must offer a significant advantage to gain approval and widespread use.

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Abbreviations

ART	Antiretroviral therapy
NRTIs	Nucleoside/nucleotide reverse transcriptase inhibitors
NNRTIs	Non-nucleoside reverse transcriptase inhibitors

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Table 1 –

Approved Nucleoside/tide Reverse Transcriptase Inhibitors

Drug	Uses	Dosing	Key Resistance Mutations	Common Adverse Effects	Key Issues Affecting Use
Zidovudine	HIV Therapy	Twice daily	M41L, D67N, K70R, L210W, T215Y, K219Q	Nausea, vomiting Anemia Mitochondrial toxicity	Significant Side Effects Twice Daily Dosing
Lamivudine / Emitricitabine	HIV Therapy PrEP	Once daily	M184V, K65R	Nail discoloration	Not very potent antiretroviral Single mutation confers resistance Generally well tolerated
Tenofovir disprovoxil fumarate*	HIV Therapy PrEP	Once daily	K65R, K70E	Bone loss Kidney dysfunction Fanconi's syndrome	Significant Long term toxicity Useful to treat HIV and Hepatitis B
Tenofovir alafenamide*	HIV Therapy	Once daily	K65R, K70E	Nausea and diarrhea	Useful to treat HIV and Hepatitis B
Stavudine	HIV Therapy	Twice daily	M41L, K65R, D67N, K70R, L210W, T215Y, K219Q	Mitochondrial toxicity Peripheral neuropathy Lipodystrophy	Significant side effects
Didanosine	HIV Therapy	Once daily	K65R, L74V	Gastrointestinal intolerance Mitochondrial toxicity Pancreatitis	Significant side effects Not available as fixed dose combination
Abacavir	HIV Therapy	Once daily	K65R, L74V, Y115F, M184V	Hypersensitivity reaction	Need for HLA B5701 testing Possible link to myocardial infarction Less effective with HIV>100,000 cpm

*Nucleotide reverse transcriptase inhibitor

PrEP=Pre-exposure Prevention Therapy

cpm=copies/mL

Table 2 –

Approved Non-Nucleoside Reverse Transcriptase Inhibitors

Drug	Uses	Dosing	Key Resistance Mutations	Common Adverse Effects	Key Issues Affecting Use
Nevirapine	HIV Therapy	Once or twice daily	Y181C, G190A, K103N	Skin Rash Hepatotoxicity	Significant Side Effects Resistance develops easily Not available in fixed dose combination
Efavirenz	HIV Therapy	Once daily	K103N, Y181C, K101P, G190A	Neuropsychiatric effects Nausea/vomiting	Significant side effects Drug-drug interactions
Etravirine	HIV Therapy	Twice daily	K101P, Y181C, L100I	Skin Rash Hepatotoxicity	Twice daily dosing Intolerance of tablets Not available in fixed dose combination
Rilpivirine	HIV Therapy	Once daily	L100I, K101P,E138A, Y181C, Y188L	Hepatotoxicity	Dosing limitations with food Cannot use with PPIs Less effective with HIV>100,000 cpm

PPIs=Proton Pump Inhibitors

cpm=copies/mL

Table 3 –

Investigational Reverse Transcriptase Inhibitors

Drug	Sponsor	Class	Clinical Trials	Dose	Activity	Resistance Features	Special Attributes
GS-9131	Gilead	NRTI	Pre-clinical	Not available	HIV-1 HIV-2	Active against K65R, L74V, M184V mutants or their combinations; Selects for Q151L mutation in HIV-1 with resistance	Once daily dosing predicted
MK-8591	Merck	NRTI	Phase 2 studies NCT03272347 * (I) NCT02217904 * (II)	0.25 mg 0.75 mg 2.25 mg	HIV-1 HIV-2	Active against K65R mutants; 9-fold reduced activity with M184V mutants	Long half-life; Weekly/Monthly dosing; Role in PrEP
Elsulfavirine (VM-1500)	Viriom	NNRTI	Phase 2 studies NCT02485509 * (I) NCT02489487 * (I) NCT02489435 * (I) NCT02489461 * (II)	20 mg 40 mg	HIV-1	Active against K103N, Y181C mutants	Long half-life; Weekly dosing; Fewer adverse events compared to Efavirenz
Doravirine (MK-1439)	Merck	NNRTI	Phase 3 studies NCT01466985 * (I) NCT01632345 * (II) NCT03272347 * (II) NCT02652260 * (II) NCT02629822 * (II) NCT02275780 * (III) NCT02403674 * (III) NCT02397096 * (III) 12 Trials Registered *	100 mg	HIV-1	Active against K103N, Y181C, and G190A mutants	Developed in Fixed dose combination with tenofovir and lamivudine; Limited side-effect profile; No dose restrictions with food or in patients with moderate liver disease

* Clinicaltrials.gov registration number

PrEP=Pre-exposure Prevention Therapy

Parentheses = Indicates Phase of Clinical Trial