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1. Introduction

In 1985, 3’-azido-thymidine (AZT, zidovudine) was identified as the first nucleoside analog with activity against human immunodeficiency virus type 1 (HIV-1) (Mitsuya et al., 1985, 1987; Mitsuya & Broder, 1986), the etiologic agent of acquired immunodeficiency syndrome (Barre-Sinoussi et al., 1983; Gallo et al., 1984). This seminal discovery showed that HIV-1 replication could be suppressed by small molecule chemotherapeutic agents, and provided the basis for the field of antiviral drug discovery. Zidovudine was approved by the United States of America Food and Drug Administration for the treatment of HIV-1 infection in 1987. In the 26 years since, an additional seven nucleoside or nucleotide analogs have been approved, while several others are in clinical development. This chapter will provide a summary of the molecular pharmacology of these compounds.

2. Mechanism of action

Retroviruses such as HIV-1 carry their genomic information in the form of (+)strand RNA, but are distinguished from other RNA viruses by the fact that they replicate through a double-stranded DNA that is integrated into the host cell’s genomic DNA (Temin & Mizutani, 1970; Baltimore, 1970; DeStefano et al., 1993). While the conversion of viral RNA into double-stranded DNA intermediate is a complex process, all chemical steps are catalyzed by the multi-functional viral enzyme reverse transcriptase (RT). HIV-1 RT exhibits two types of DNA polymerase activity, an RNA-dependent DNA polymerase activity that synthesizes a (-)strand DNA copy of the viral RNA, and a DNA-dependent DNA polymerase activity that generates the (+)strand DNA (Peliska & Benkovic, 1992; Cirno et al., 1995). RT also has ribonuclease H activity that degrades the RNA in the intermediate (+)RNA/(-)DNA duplex (Ghosh et al., 1997).

Once metabolized by host cell enzymes to their triphosphate forms (described in more detail below), nucleoside analogs inhibit HIV-1 reverse transcription. As such, they are typically referred to as nucleoside RT inhibitors (NRTI). NRTI-triphosphates (NRTI-TP) inhibit RT-catalyzed proviral DNA synthesis by two mechanisms (Goody et al., 1991). First, they are
competitive inhibitors for binding and/or catalytic incorporation with respect to the analogous natural dNTP substrate. Second, they terminate further viral DNA synthesis due to the lack of a 3’-OH group. Chain termination is the principal mechanism of NRTI antiviral action (Goody et al., 1991). In theory, NRTI-TPs should be ideal antivirals. Each HIV virion carries only two copies of genomic RNA. There are about 20,000 nucleotide incorporation events catalyzed by RT during the synthesis of complete viral DNA, thus providing about 5000 chances for chain-termination by any given NRTI. Since HIV-1 RT lacks a formal proof-reading activity, a single NRTI incorporation event should effectively terminate reverse transcription. In reality, however, NRTIs are less potent than might be expected. The two primary reasons responsible for this are: (i) HIV-1 RT can effectively discriminate between the natural dNTP and NRTI-TP, and the extent of this discrimination is dramatically modulated by nucleic acid sequence (Isel et al., 2001); and (ii) HIV-1 RT can excise the chain-terminating NRTI-monophosphate (NRTI-MP) by using either pyrophosphate (pyrophosphorolysis) or ATP as a substrate (Meyer et al., 1998; Goldschmidt & Marquet, 2004).

3. NRTI approved for clinical use

3.1 Zidovudine

Zidovudine was first synthesized in 1964 as a potential anticancer drug, but was not further developed for human use because of toxicity concerns. However, as described in the Introduction, it was found to have potent anti-HIV activity and, in 1987, was the first antiviral drug to be approved for clinical use. Zidovudine is a thymidine analog in which the 3’-OH group has been replaced with an azido (-N3) group (Figure 1). Zidovudine permeates the cell membrane by passive transport and not via a nucleoside carrier transporter (Zimmerman et al., 1987). It has good oral bioavailability and shows efficient penetration into the central nervous system. Zidovudine is efficiently metabolized to its 5’-MP form by cytosolic thymidine kinase (Ho & Hitchcock, 1989). The phosphorylation of zidovudine-MP to zidovudine-DP is catalyzed by thymidinylate monophosphate kinase (dTMP kinase; Furman et al., 1986). Interestingly, the apparent Michaelis constant (K_m) of zidovudine-MP for dTMP kinase is almost equivalent to that of dTMP, however its maximum kinetic rate (V_{max}) is only 0.3 % that of dTMP (Furman et al., 1986). Therefore, zidovudine-MP acts as a substrate inhibitor of dTMP kinase and limits its own conversion to the 5’-DP form. In this regard, there is a marked accumulation of zidovudine-MP and only low levels of the 5’-DP- and 5’-TP derivatives are detected in human T-lymphocytes (Balzarini et al., 1989). Cellular nucleoside diphosphate kinase (NDP kinase) is likely responsible for the further conversion of zidovudine-DP to zidovudine-TP. Zidovudine is metabolized to its 5’-O-glucuronide in the liver, kidney, and intestinal mucosa (Barbier et al., 2000). Because of the extensive glucuronidation of ZDV, other drugs that are also glucuronidated or that inhibit this process cause an increase in zidovudine plasma levels. Fourteen percent of the parent compound and 74% of the glucuronide have been recovered from the urine after oral administration in normal subjects (Ruane et al., 2004). Renal excretion of zidovudine is by both glomerular filtration and active tubular secretion. In some cells zidovudine can be metabolized to the highly toxic reduction product 3’-amino-thymidine (Weidner & Sommadossi, 1990).
3.2 Stavudine

Like zidovudine, stavudine (2',3'-didehydro-3'-deoxythymidine, d4T) is a thymidine analog that undergoes metabolic activation by the sequential action of thymidine kinase and dTMP kinase (Figure 1). However, stavudine is inefficiently phosphorylated to its 5'-MP form by thymidine kinase (August et al., 1988; Zhu et al., 1990). As such, this first phosphorylation step is rate-limiting and most intracellular stavudine is not phosphorylated (Balzarini et al., 1989). Maximal plasma concentrations of stavudine are achieved within 2 hours of oral administration and increase linearly as the dose increases, with an absolute bioavailability approaching 100 % (Rana & Dudley, 1997). The drug distributes into total body water and appears to enter cells by non-facilitated diffusion (passive transport). Penetration into the central nervous system, however, is far less than zidovudine. Stavudine is cleared quickly with a terminal plasma half-life of 1-1.6 hours by both renal and nonrenal processes (Dudley et al., 1992).

3.3 Didanosine

Initially, 2',3'-dideoxyadenosine (ddA) was evaluated as a clinical candidate but was ultimately discovered to cause nephrotoxicity. ddA is acid labile and oral administration leads to exposure to the acidic pH of the stomach and degradation to adenine (Masood et al., 1990). Adenine is further metabolized to 2,8-dihydroxyadenine which causes nephrotoxicity by crystallization in the kidney. Interestingly, ddA was shown to be metabolized to 2',3'-dideoxyinosine (ddl, didanosine) by adenosine deaminase (Figure 2), and that much of the antiviral activity of ddA resides in didanosine (Cooney et al., 1987). Furthermore, the administration of didanosine avoids the production of adenine and the resulting nephrotoxicity. Didanosine is phosphorylated to didanosine-MP by cytosolic 5’-nucleotidase, which uses either inosine monophosphate (IMP) or guanosine monophosphate (GMP) as
phosphate donors (Johnson & Fridland, 1989). Didanosine-MP is then converted to ddAMP by adenylosuccinate synthetase and 5'-adenosine monophosphate-activated protein (AMP) kinase (Ahluwalia et al., 1987). The enzymes involved in phosphorylation of ddAMP to ddADP and ddATP have not been identified, although AMP kinase and NDP kinase have been proposed to play a role. ddATP is the active metabolite that is recognized by HIV-1 RT and incorporated into the nascent viral DNA chain causing chain-termination. No evidence has been provided for the formation of didanosine-DP or didanosine-TP. Didanosine is hydrolyzed to hypoxanthine by purine nucleoside phosphorylase (PNP) and further anabolized by hypoxanthine-guanine phosphoribosyl transferase to IMP (Ahluwalia et al., 1987). ATP and GTP are formed from IMP through the classical purine nucleotide biosynthetic pathways.

Fig. 2. Metabolic pathways of ddA and didanosine

3.4 Lamivudine and emtricitabine

The structurally related cytidine analogs lamivudine ((-)-3'-thia-2',3'-dideoxycytidine; 3TC) and emtricitabine ((-)-3'-thia-5-flouro-2',3'-dideoxycytidine; FTC) both contain the unnatural L-enantiomer ribose with a sulfur atom replacing the C3' position (Figure 3). Emtricitabine has an additional 5-flouro moiety on the cytosine ring. Lamivudine and emtricitabine are both metabolized to their respective 5'-mono- and di- and triphosphate derivatives by deoxycytidine kinase, deoxycytidine monophosphate kinase, and 5'-nucleoside diphosphate kinase, respectively (Chang et al., 1992; Cammack et al., 1992; Stein & Moore 2001; Darque et al., 1999; Bang & Scott, 2003). There is no evidence that lamivudine or emtricitabine are deaminated to their uridine analogs by cellular cytidine or deoxycytidine deaminases (Starnes & Cheng, 1987). Formation of the free base by cellular pyrimidine phosphorylases has also not been observed. Lamivudine-DP and emtricitabine-TP accumulate to higher levels in peripheral blood mononuclear cells than their monophosphate forms. It has been suggested that conversion of lamivudine-DP to lamivudine-TP is rate limiting. Lamivudine and emtricitabine are rapidly absorbed through
the GI tract with peak plasma levels of 85-93% achieved within 2 hours post oral administration. Lamivudine has a plasma half-life of 5-7 hours and is eliminated unmetabolized by active organic cationic excretion (Johnson et al., 1999). Emtricitabine persists in plasma with a half-life of 10 hours and is eliminated primarily in urine by glomerular filtration and active tubular secretion but approximately 14% is eliminated in feces. Oxidation of the 3’-thiol by unidentified enzymes yields 3’-sulfoxide diastereomers and 2’-O-glucuronidation also occurs.

Fig. 3. Metabolic pathways of lamivudine and emtricitabine

3.5 Abacavir

Abacavir (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]cyclopent-2-en-1-yl)methanol) is a prodrug of carbovir (2-Amino-1,9-dihydro-9-[(1R,4S)-4-(hydroxymethyl)-2-cyclopenten-1-yl]-6H-purin-6-one), a deoxyguanosine analog (Figure 4; Daluge et al., 1997). Abacavir permeates T lymphoblastoid cell lines by passive diffusion. Abacavir is phosphorylated to abacavir-MP by adenosine phosphotransferase (Faletto et al., 1997). A yet unidentified cytosolic deaminase then converts abacavir-MP to carbovir-MP. Phosphorylation to the diphosphate derivative occurs via guanylinylate monophosphate kinase. The final phosphorylation step can be catalyzed by a number of cellular enzymes including 5’-nucleotide diphosphate kinase, pyruvate kinase, and creatine kinase (Faletto et al., 1997). A linear dose relationship with carbovir-mono-, di-, and tri- phosphate derivatives over a 1000-fold dose range in vitro suggests there are no rate limiting steps in abacavir anabolism. The active metabolite carbovir-TP has been shown to persist with an elimination half-life of greater than 20 hours (McDowell et al., 2000). Abacavir bioavailability is ~83 % and is rapidly absorbed after oral dosing reaching peak plasma levels within 1 hour (Chittick et al., 1999). However, abacavir is extensively catabolized in the liver and only 1.2% is excreted as unchanged abacavir in urine. Abacavir oxidation by alcohol dehydrogenases to form the 5’-carboxylic acid derivative represents 36% of metabolites recovered from urine, while the 5’-O-glucuronide corresponds to 30% of metabolites from urine (Chittick et al., 1999). Fecal excretion also accounts for approximately 16 % of the given dose. Abacavir is not metabolized by cytochrome P450 enzymes and does not inhibit these enzymes.
3.6 Tenofovir and tenofovir disoproxil fumerate

The acyclic nucleoside phosphonate tenofovir (R-9-(2-phosphonylmethoxypropyl)-adenine) has no sugar ring structure but contains an acyclic methoxypropyl linker between the base N9 atom and a non-hydrolyzable C-P phosphonate bond. Thus tenofovir represents the only currently approved nucleotide HIV inhibitor. Tenofovir is poorly absorbed by the oral route and is therefore administered as a lipophilic orally bioavailable prodrug tenofovir disoproxil fumerate (TDF), a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester of tenofovir (Figure 5). TDF is readily absorbed by the gastrointestinal epithelial cells with an oral bioavailability of 25% (Barditch-Crovo et al., 2001). Administration with a high fat meal increases absorption to 40%. Degradation of TDF to its monoester and subsequently to tenofovir occurs readily in the intestinal mucosa by the action of carboxylesterases and phosphodiesterases, respectively. The mono- or bis-ester forms of tenofovir are not observed in plasma suggesting efficient release of tenofovir following oral administration of TDF (Naesens et al., 1998). Following oral administration tenofovir has a long terminal half-life of 17 hours. The phosphonic acid linkage is chemically and metabolically stable and phosphorolysis back to the nucleoside does not occur (Naesens et al., 1998). Tenofovir is rapidly converted intracellularly to tenofovir-monophosphate and the active tenofovir-diphosphate forms by adenylyl monophosphate kinase and 5'-nucleoside diphosphate kinase, respectively (Robbins et al., 1998). Tenofovir is not subject to intracellular deamination or deglycosylation. This stability results in a very long intracellular half-life for tenofovir-diphosphate of 15 hours in activated lymphocytes and 50 hours in resting lymphocytes (Robbins et al., 1998). Tenofovir is eliminated by glomerular filtration and active tubular secretion by organic anion transporter mediated uptake and MRP4 mediated efflux (Ray et al., 2006). At 72 hours post oral administration 70 - 80 % is recovered from urine as unchanged tenofovir. Tenofovir does not inhibit cytochrome P450 enzymes.

Fig. 4. Metabolic pathways for abacavir
However, the mono- and di-phosphate forms both inhibit purine nucleoside phosphorylase which is responsible for base removal of didanosine to form hypoxanthine.

Fig. 5. Metabolic pathways of tenofovir and TDF

4. NRTI in the pipeline

Despite the widespread clinical success of NRTI-containing therapy, the currently FDA approved NRTIs display important limitations including the selection of drug resistance mutations that display cross-resistance to other NRTI, toxicity-related adverse events, and drug-drug interactions (for review see Cihlar & Ray, 2010). Thus, there is a need for novel NRTI that overcome these limitations. Here we will discuss the pharmacology of several novel drug candidates.

4.1 Apricitabine

Apricitabine (ATC) is the (-)-enantiomer of 2’-deoxy-3’-oxa-4’-thiocytidine, a deoxycytidine analog that is currently in phase II/III clinical trials (Figure 6). Both the (+) and (-)-enantiomers of apricitabine demonstrate potent inhibition of HIV-1 replication, however the (+)-enantiomer demonstrated significant mitochondrial and cellular toxicity in pre-clinical studies that was not observed with the (-) enantiomer (de Muys et al., 1999; Taylor et al., 2000). Racemic conversion of (-)-apricitabine to (+)-apricitabine is not observed in vivo (Holdich et al., 2006). Orally administered ATC is absorbed quickly, reaching maximal plasma levels within 2 hours with a plasma half-life of 3 hours. Maximal peripheral blood mononuclear cell (PBMC) intracellular concentrations of apricitabine -TP are achieved 3.5 – 4 hours after oral administration in healthy and HIV-infected patients. The intracellular half-life is 6 – 7 hours (Sawyer & Struthers-Semple, 2006; Cahn et al., 2008; Holdich et al., 2007). Apricitabine is not metabolized by hepatocytes in vitro, however a deaminated metabolite was observed likely due to gastrointestinal metabolism (Nakatani-Freshwater et al., 2006). This metabolite is excreted renally and does not demonstrate antiviral or pharmacologic effects. Apricitabine had no effect on cytochrome P450 or glucuronidase but was a weak inhibitor of P-glycoprotein (Sawyer & Cox, 2006). The first phosphorylation of apricitabine is
mediated by deoxycytidine kinase, the enzyme also responsible for the initial phosphorylation of lamivudine and emtricitabine (de Muys et al., 1999). The possibility of competition for deoxycytidine kinase was examined in PBMC. Co-administration of apricitabine with lamivudine or emtricitabine leads to a dose-dependent decrease in apricitabine phosphorylation, whereas lamivudine and emtricitabine phosphorylation was not affected by apricitabine (Bethell et al., 2007). In healthy volunteers given apricitabine and lamivudine, the intracellular PBMC levels of apricitabine-TP were decreased 75% compared to apricitabine alone (Holdich et al., 2006). Consequently, administration of apricitabine in combination with lamivudine or emtricitabine is not recommended. Similarly, lamivudine and emtricitabine co-administration is also contraindicated. Apricitabine-MP is sequentially phosphorylated to the di- and tri-phosphate forms by cytidine or deoxycytidine monophosphate kinase and 5'-nucleotide diphosphate kinase, respectively.

Fig. 6. Metabolic pathway of apricitabine

### 4.2 Festinavir

Festinavir (2',3'-didehydro-3'-deoxy-4'-ethynylthymidine; 4'-Ed4T) is a 4'-ethynyl analog of stavudine that is 5-10 fold more potent (Figure 7) (Haraguchi et al., 2003; Nitanda et al., 2005). Festinavir shows decreased cellular toxicity compared to stavudine, with little or no inhibition of host polymerases (Yang et al., 2007; Dutschman et al., 2004). Stepwise phosphorylation of festinavir occurs via the same enzymes as stavudine. Thymidine kinase 1 phosphorylates festinavir to festinavir-MP with 4-fold greater efficiency than stavudine (Hsu et al., 2007). The efficiency of festinavir-MP phosphorylation by thymidinylate monophosphate kinase is approximately 10% of that seen for stavudine-MP or zidovudine-MP. Conversion from festinavir-DP to festinavir-TP appears to be catalyzed by multiple enzymes including nucleoside diphosphate kinase, pyruvate kinase, creatine kinase, and 3-phosphoglycerate kinase (Hsu et al., 2007). In contrast to other thymidine analogs which are readily catabolized by thymidine phosphorylase, festinavir catabolism cannot be detected. Furthermore, festinavir efflux from the cell is much less efficient than that of zidovudine. The festinavir nucleoside form alone is effluxed by a yet to be identified cellular transporter, while zidovudine and zidovudine-MP are effluxed from the cell. A Phase 1a study investigated the pharmacokinetic profile of a single oral dose between 10 and 900 mg and found a linear dose response in plasma with no apparent effects from food (Paintsil et al., 2009). A Phase 1b/2a study of festinavir oral monotherapy in 32 patients was recently completed. The results indicated that festinavir was safe (few festinavir related adverse events), well tolerated, and demonstrated dose dependent decreases in viral load between 0.87 and 1.36 logs (Cotte et al., 2010).
The purine nucleoside analog 1-β-D-dioxolane guanosine (DXG) has potent activity against HIV and hepatitis B virus (Kim et al., 1993). However, it demonstrates poor solubility and limited oral bioavailability in monkeys (Chen et al., 1996). The analog 1-β-D-2,6-diaminopurine dioxolane (amdoxovir; Figure 8) also exhibits antiviral activity and is more water soluble and orally bioavailable (Chen et al., 1999; Kim et al., 1993). Amdoxovir serves as a prodrug for DXG by deamination at the 6-position by adenosine deaminase (Gu et al., 1999). In vitro, amdoxovir bound adenosine deaminase as efficiently as adenosine, however amdoxovir was deaminated 540-fold slower than adenosine (Furman et al., 2001). Only DXG-triphosphate was detected in PBMC and CEM cells following exposure to DXG or amdoxovir (Rajagopalan et al., 1994; Rajagopalan et al., 1996). DXG is phosphorylated to DXG-MP by 5′-nucleotidase using IMP as a phosphate donor (Feng et al., 2004). DXG-diphosphate is then generated by guanosine monophosphate kinase (GMP kinase). DXG-DP acts as substrate for phosphorylation to the active DXG-TP for several enzymes including nucleotide diphosphate kinase (NDP kinase), 3-phosphoglycerate kinase (3-PG kinase, creatine kinase, and pyruvate kinase. Amdoxovir is rapidly converted to DXG in monkeys, woodchucks, and rats with approximately 61% of the dose converted to DXG (Chen et al., 1996; Chen et al., 1999; Rajagopalan et al., 1996). The oral bioavailability of amdoxovir is estimated to be 30% (Chen et al., 1999). Following oral administration of amdoxovir to HIV-infected patients, peak plasma levels of amdoxovir and DXG were reached within 2 hours.
(Thompson et al., 2005). Amdoxovir was eliminated from plasma with half-life of 1 - 2 hours by conversion to DXG, whereas DXG demonstrated a longer half-life of 4 - 7 hours. In animal studies amdoxovir toxicities included obstructive nephropathy, uremia, islet cell atrophy, hyperglycemia, and lens opacities (Rajagopalan et al., 1996). In a phase I/II clinical study 4 of 18 patients developed nongradeable lens opacities (Thompson et al., 2005). In other studies most adverse events were minor and included nausea, headache, and diarrhea (Gripshover et al., 2006; Murphy et al., 2008).

4.4 GS-7340

GS-7340 (9-[(R)-2-[[S]-1-(isopropoxycarbonyl)ethyl]amino]phenoxyposphinyl]-methoxy]propyl]adenine) is a novel isopropylalaninyl phenyl ester prodrug of tenofovir designed to increase intracellular delivery of the active tenofovir-DP metabolite by masking the charged phosphonate (Figure 9; Eisenberg et al 2001). Preclinical studies demonstrated 200-fold improved plasma stability and 400-fold increased accumulation of tenofovir and active tenofovir-DP in lymphatic tissues and peripheral blood mononuclear cells (PBMC) compared to tenofovir (Lee et al., 2005; Eisenberg et al., 2001). GS-7340 has 1000-fold improved potency in vitro over tenofovir. Following rapid target cell uptake, GS-7340 is hydrolyzed at the carboxy ester bond in lysosomes by the serine protease cathepsin A and other serine and cysteine proteases (Birkus et al., 2007; 2008). The resulting partially stable product spontaneously releases phenol by intramolecular cyclization and hydrolysis to a negatively charged, cell impermeable tenofovir-alanine intermediate (Balzarini et al., 1996). Formation of tenofovir-alanine is faster in resting PBMC compared to activated PBMC, while metabolism to parent tenofovir by a phosphoamidase and downstream phosphorylation to tenofovir-MP and tenofovir-DP is much faster in activated PBMC. A recent clinical study comparing 50 mg and 150 mg doses of GS-7340 with 300 mg TDF was conducted to determine the efficacy, safety and pharmacokinetics over 14 days (Markowitz et al., 2011). Viral loads were reduced -1.71-log and -1.57-log for 150 mg and 50 mg doses, respectively, compared to 0.94-log for TDF. PBMC levels of tenofovir were 4 – 33- times greater with GS-7340 than those for TDF at day 14 while plasma levels of tenofovir were decreased up to 88% at 24 hours with administration of GS-7340 compared to TDF. No serious adverse events were reported while the most frequent complaint was mild to moderate headache and nausea.

4.5 CMX-157

Like GS-7340, CMX-157 is an alternative prodrug of tenofovir designed to increase cell penetration by the natural lipid uptake pathways (Figure 9; Hostetler et al., 1997; Painter et al., 2004). CMX-157 contains a hexadecyloxypropyl (HDP) lipid conjugation which mimics lysophosphatidylcholine. CMX-157, unlike TDF is not cleaved to free tenofovir in the intestinal mucosa and thus circulates in plasma as the tenofovir-HDP lipid conjugate (Painter et al., 2007). Tenofovir-HDP is not a substrate for human organic anion transporters and therefore is subject to decreased renal excretion and increased intracellular drug exposure compared to TDF (Tippin et al., 2010). Free tenofovir is liberated intracellularly by hydrolytic removal of the HDP lipid by phospholipases. Intracellular activation to the active tenofovir-DP form is achieved in the same manner as TDF. CMX-157 delivers > 30-fold increased active metabolite tenofovir-DP in PBMC than tenofovir. Higher intracellular
concentrations of CMX-157 provide >300-fold greater activity against clinical isolates than tenofovir with EC$_{50}$ values < 1 nM (Lanier et al., 2010). It has additionally been proposed that CMX-157 may bind cell free virions by direct lipid insertion into the viral envelope resulting in facilitated delivery to target cells (Painter et al., 2007). CMX-157 recently completed a Phase I clinical trial to evaluate safety, tolerability and pharmacokinetics. CMX-157 was well tolerated with no drug-related adverse events. Plasma levels increased linearly with dose and active TFV-DP was detected up to six days post administration of a 400 mg dose suggesting the possibility of a once weekly dosing regimen.

Fig. 9. Intracellular metabolism of GS-7340 and CMX-157

5. Conclusions

Nucleoside and nucleotide reverse transcriptase inhibitors have remained the backbone of antiretroviral therapy. The absolute dependence of NRTI on host cellular enzymes for activation is a unique property of this drug class. The eight approved NRTI and numerous experimental NRTI display great diversity for all of these factors, thus presenting pharmacological advantages and challenges that are unique to the NRTI class. The complex relationships between NRTIs and host cell enzymes have necessitated detailed studies of the in vitro and in vivo pharmacologic properties of novel NRTIs in pre-clinical development. Current drug discovery efforts increasingly utilize NRTI prodrugs in order to accelerate NRTI phosphorylation or otherwise improve pharmacologic properties. Further understanding of the cellular pharmacology of NRTI is crucial for the development of novel drugs for increased potency, improved safety and tolerability, and decreased resistance.
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7. References


The history of pharmacology travels together to history of scientific method and the latest frontiers of pharmacology open a new world in the search of drugs. New technologies and continuing progress in the field of pharmacology has also changed radically the way of designing a new drug. In fact, modern drug discovery is based on deep knowledge of the disease and of both cellular and molecular mechanisms involved in its development. The purpose of this book was to give a new idea from the beginning of the pharmacology, starting from pharmacodynamic and reaching the new field of pharmacogenetic and ethnopharmacology.

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