

REVIEW

## Zidovudine and Lamivudine for HIV Infection

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**Abstract:** Zidovudine and lamivudine (ZDV and 3TC) are long-standing nucleoside analog-reverse transcriptase inhibitors (NRTIs) with extensive clinical experience in a wide spectrum of patients from in utero through childhood and adult ages. The safety profiles of both drugs are well-known and side effects for ZDV most commonly include nausea/vomiting, fatigue, anemia/neutopenia, and lipoatrophy; while 3TC is well-tolerated. ZDV-3TC is currently a viable alternative NRTI backbone for initial three-drug therapy of HIV infection when tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) cannot be used because of a relative or absolute contraindication. ZDV-3TC continue to be viable alternatives for children, pregnant women and in resource limited settings where other recommended options are not readily available. ZDV-3TC penetrate the Central Nervous System (CNS) well, which makes ZDV-3TC attractive for use in patients with HIV-associated neurological deficits. Additional benefits of these drugs may include the use of ZDV in combination with certain NRTIs to exert selective pressure to prevent particular drug resistance mutations from developing, and giving a short course of ZDV-3TC to prevent resistance after prophylactic single dose nevirapine.

**Keywords:** zidovudine, lamivudine, HIV

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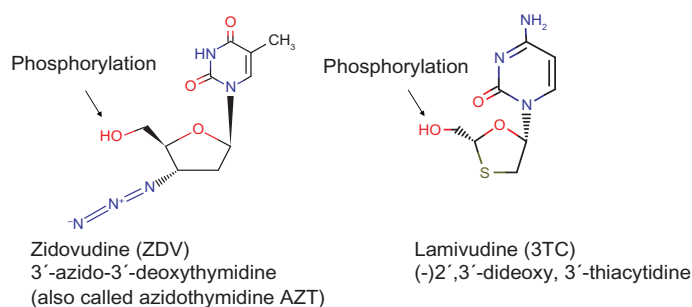
## Introduction

Zidovudine (ZDV) and lamivudine (3TC) have long and distinguished histories among the 24 drugs now available to treat HIV-infection.<sup>1</sup> These nucleoside analog reverse transcriptase inhibitors (NRTIs) were front and center during the evolution of antiretroviral therapy over past two decades from treatment with single NRTI agents, followed by dual NRTIs, to combinations of three active drugs from at least two drug classes; referred to as ART or highly active antiretroviral therapy (HAART).<sup>1</sup> ART has revolutionized the prognosis of HIV from a fatal disease to a manageable chronic condition. ZDV and 3TC enjoyed several years as the NRTI backbone of first choice for ART regimens in antiretroviral naïve patients based on favorable efficacy and safety information from multiple randomized controlled clinical trials.<sup>2-4</sup> However, newer NRTIs have become available with improved tolerability and efficacy compared with the ZDV-3TC combination, based on randomized clinical trial data, which has led to the recommendation of tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) as the NRTI backbone standard of care in antiretroviral naïve patients today (plus either efavirenz, raltegravir, or ritonavir-enhanced darunavir or atazanavir).<sup>5</sup> While 3TC is relatively well-tolerated, the tolerability issues with ZDV can be troublesome and include lipodystrophy, anemia/neutropenia, nausea, fatigue, and headache.<sup>6-8</sup> Nevertheless, ZDV-3TC remains among the multiple alternative regimens advocated in circumstances when the combination of TDF-FTC is not the best option for the particular patient. ZDV and 3TC are also prominently used in special clinical settings such as in individuals with resistant virus and as pre- and post-exposure prophylaxis, especially for pregnant women and infants born to HIV-infected mothers.<sup>5,9,10</sup> A unique consideration for ZDV and 3TC is their long-term safety histories, which are among the best understood among the antiretroviral agents used today.

## Pharmacology

### Mechanism of pharmacologic action

ZDV and 3TC are nucleoside analog reverse transcriptase inhibitors (Fig. 1). Both drugs require phosphorylation intracellularly to the triphosphate anabolite



**Figure 1.** Chemical structures for ZDV and 3TC. From the National Library of Medicine USA.

for pharmacologic activity. The drug-triphosphate interferes with HIV reverse transcriptase by competing with natural nucleotides for incorporation into the growing HIV DNA chain, and terminating HIV DNA chain elongation if taken up because the drugs lack the 3' hydroxyl on the deoxyribose ring necessary for the sugar-phosphate linking (Fig. 1).<sup>11,12</sup> HIV-DNA synthesis is a pivotal and necessary stage in the viral replication cycle and inhibition of this step effectively halts viral propagation. Both 3TC and ZDV have activity against different subtypes of wild-type HIV-1 and both are also active against HIV-2, although the effectiveness in HIV-2 infected patients is not fully established.<sup>13-15</sup> The *in vitro* 50% effective concentration ( $EC_{50}$ ) against HIV-1 is approximately 1  $\mu$ M (230 ng/mL) for 3TC and 0.01  $\mu$ M (2.7 ng/mL) for ZDV, but several factors influence this value such as the cell-type used for the assay and the subtype of HIV-1 or HIV-2 studied.<sup>8</sup> As one measure of potency *in vivo*, ZDV monotherapy reduces HIV-RNA in plasma of antiretroviral naïve individuals by about 0.85  $\log_{10}$  copies/mL whereas 3TC monotherapy reduces plasma HIV-RNA by about 1.5  $\log_{10}$  copies/mL.<sup>16,17</sup> Compared with other antiretroviral drugs, these measures of potency are on the lower end for ZDV, versus about average for 3TC.<sup>18-21</sup>

ZDV shows broad spectrum activity among subfamilies of retroviruses including Spumavirinae, Lentivirinae and the Oncovirinae *in vitro*; but 3TC activity is not as broad.<sup>22</sup> This information is consistent with the observation that reverse transcriptase is the most highly conserved element across retroviruses.<sup>23</sup> These findings may be of significance as certain diseases in man are attributed to retroviral infections such as primary biliary cirrhosis (possible



betaretrovirus) and chronic fatigue syndrome (possible gammaretrovirus).<sup>24,25</sup> 3TC is active against hepatitis B virus and is used for HBV infection at a lower dose. ZDV has been used in combination with interferon as an anti-leukemic drug, although the oncolytic mechanism of action is not well-understood.<sup>26</sup>

### Unintended pharmacologic effects

NRTIs including ZDV and 3TC are associated with several unintended pharmacologic effects. The best described is the apparent inhibition of mitochondrial DNA polymerase gamma, a problem of non-specificity whereby the drug-triphosphate interferes with mitochondrial DNA replication in the same manner as inhibition of HIV DNA replication.<sup>27</sup> This non-specificity leads to reduced mitochondrial DNA, lower RNA and protein output, and mitochondrial dysfunction with anaerobic respiration, lactic acid production, oxidative damage, and clinical symptoms.<sup>27-29</sup> ZDV has been associated with more frequent and severe mitochondrial toxicity compared with 3TC. ZDV toxicities include myopathy with red-ragged fibers rarely including cardiomyopathy, loss of subcutaneous fat, anemia/neutropenia, bone loss, and lactic acidosis with hepatosteatosis.<sup>30-34</sup> Of these, myopathy, lipoatrophy, and lactic acidosis with hepatosteatosis have been attributed to mitochondrial toxicity in origin based on pathologic evidence of abnormal mitochondrial structure, or depleted mitochondrial DNA or RNA.<sup>29,30,32</sup> All NRTIs including ZDV and 3TC carry warnings for lactic acidosis with hepatosteatosis, a rare but life-threatening mitochondrial toxicity.

The molecular biology of NRTI-associated mitochondrial toxicity is complicated by several issues especially for ZDV. First, HIV-disease itself appears to have a negative impact on mitochondria. For instance, HIV-infected antiretroviral naïve individuals have lower mitochondrial DNA copies in peripheral blood mononuclear cells (PBMCs) compared with HIV-uninfected individuals.<sup>35</sup> Secondly, ZDV has a low propensity for inhibiting mitochondrial DNA polymerase gamma in vitro, which casts doubt on the traditional “polymerase gamma” theory for ZDV described above.<sup>28,36-38</sup> The in vitro studies that support the “polymerase gamma” theory apply more readily to d4T, ddI, and ddC compared with ZDV because these drugs inhibit polymerase gamma

over 1000-fold more efficiently compared with ZDV (approximate potency: ddC > ddI > d4T >> 3TC > TFV > ZDV >> ABC).<sup>37</sup> Furthermore, the constellation of toxicity symptoms for the potent “polymerase gamma” inhibitors (d4T, ddI, and ddC) are different than for ZDV and include peripheral neuropathy and pancreatitis (as well as lipoatrophy for d4T). Given that the intracellular anabolism for ZDV and d4T are similar, it is not clear why these drugs have differences in tissue selectivity for mitochondrial toxicity (muscle for ZDV and nerve and pancreas for d4T). This suggests that the mechanism of toxicity for d4T and ZDV may differ.<sup>38</sup> Overall, the tissue selectivity of mitochondrial toxicity is not well understood, but may be associated with different drug-phosphate accumulation patterns by tissue type based on the expression of enzymes that govern drug-phosphate disposition (transporters, kinases, nucleotidases, etc).<sup>36,39</sup> The exact mechanism of cellular toxicity for ZDV may include ZDV’s propensity to inhibit deoxythymidine-triphosphate production and concentration in mitochondria; inhibition of the ADP-ATP translocator in the mitochondrial membrane; and direct toxicity from ZDV-monophosphate.<sup>40,41</sup> 3TC is not considered among the mitochondrial toxins. While it is efficiently taken up by polymerase gamma and incorporated into growing mitochondrial DNA, it is very efficiently excised from the DNA by the exonuclease function of polymerase gamma.<sup>12,37</sup> 3TC has extensive and favorable safety and tolerability profile based on years of clinical experience.<sup>5</sup>

There has been concern about the long-term carcinogenic potential of ZDV and 3TC given that they are mutagenic in vitro and ZDV is weakly carcinogenic in mice.<sup>8,42</sup> This is of high relevance especially for using these agents in infants and pregnant women, which is common practice to prevent HIV transmission from mothers to infants. The evidence to date, however, does not show a signal for teratogenicity or carcinogenicity in humans. One study assessed cancer rates in 9127 HIV-uninfected children born to HIV-infected mothers and exposed to ZDV and 3TC, as well as other antiretroviral drugs.<sup>43</sup> The average age of the cohort was 5.4 years, which translated to 53052 person-years of follow up. Cancer rates were compared with national registries of childhood cancers. 10 cases were observed in children exposed



to NRTIs versus about 9 cases in national registries (incidence ratio of about 1.0). The relative risk of cancer was higher in children exposed to ddI-3TC compared with ZDV monotherapy, but the non-elevated cancer rate overall complicates the interpretation of this finding. Other studies have raised the specter of mitochondrial toxicity in infants exposed to ZDV-3TC with manifestations including cardiomyopathy and CNS dysfunction.<sup>44</sup> However, the studies are not uniform in their findings and the observational designs may not include appropriate control groups such as HIV-uninfected infants born to HIV-infected mother who are not exposed to NRTIs, as well as not being able to adjust for all potential confounding factors.<sup>45</sup> One finding that is clear from infant studies is the well-known reversible hematologic toxicity from ZDV and ZDV-3TC.<sup>44</sup> In terms of teratogenicity in humans, information from the Antiretroviral Pregnancy Registry ([http://www.apregistry.com/forms/interim\\_report.pdf](http://www.apregistry.com/forms/interim_report.pdf)), which monitors birth defects associated with antiretroviral drugs, has accumulated enough ZDV-3TC exposures during pregnancy to rule out a 1.5-fold elevated risk of birth defects. The registry has not detected an increase in birth defects for ZDV or 3TC to date. In summary, the short-to-medium-term carcinogenicity and teratogenicity profiles of ZDV-3TC appear reassuring, nevertheless continued follow-up is needed to further define the long-term safety profile.

## Clinical pharmacokinetics

### Plasma profiles

The bioavailability of ZDV is about 64%.<sup>8</sup> Absorption is rapid with peak concentrations occurring about 1 hour post dose. Food delays, but does not significantly impair the extent of absorption. Approximately 14% of a ZDV dose is eliminated as unchanged drug in urine and 74% is glucuronidated by UGT2B7 to the ZDV 5'-O-glucuronide, which is then eliminated in urine.<sup>8,46</sup> Individuals who carry the UGT2B7 \*1c variant (c.735A > G) were shown to exhibit 200% faster oral clearance compared with non-carriers in a small study among tuberculosis-coinfected and -cotreated individuals from Ghana.<sup>47</sup> The clinical implications of this pharmacogenetic difference are not known and confirmatory studies will be needed in broader populations. A small fraction of ZDV is metabolized by other

microsomal pathways (possibly CYP2C9) to a 3' amino metabolite, which has been implicated in hematologic toxicities in some studies.<sup>48,49</sup> ZDV phosphorylation is estimated to contribute only 1% to ZDV clearance.<sup>50</sup> ZDV exhibits two-compartment pharmacokinetics, but a one-compartment model adequately characterizes ZDV pharmacokinetics in patients.<sup>51</sup> The terminal plasma half-life is about 1 hour. ZDV dose adjustments are recommended for severe renal impairment.<sup>52</sup> In terms of hepatic disease, no dosing changes are recommended for ZDV in spite of evidence of slower drug clearance in patients with significant liver impairment; thus these patients should be monitored closely.<sup>53</sup>

Unlike drugs from the protease inhibitor or non-nucleoside reverse transcriptase classes, NRTIs have few drug-drug interaction concerns.<sup>5</sup> For ZDV, drug-drug interaction considerations include pharmacodynamic issues as with additive bone marrow suppression with ganciclovir or ribavirin; reduced clearance of ZDV through inhibition of UGT2B7 as with valproic acid; or antagonistic phosphorylation interactions as with stavudine. A good reference for drug interactions can be found at the following website ([http://www.hiv-druginteractions.org/frames.asp?drug/drg\\_main.asp](http://www.hiv-druginteractions.org/frames.asp?drug/drg_main.asp)) and in the US Department of Health and Human Services guidelines for using antiretroviral drugs in adults and adolescents.<sup>5</sup>

ZDV penetrates certain relevant body fluids at high concentrations such as CNS and genital secretions. For instance, ZDV concentrations in cerebral spinal fluid (CSF) are approximately 60% the concentrations in plasma, although the ratio changes significantly over the dose interval probably because the CSF fluid turnover rate is slow compared with plasma clearance.<sup>8,54</sup> There is uncertainty about how CSF drug concentrations correspond with brain tissue penetration, but ZDV therapy has been associated with neurologic improvements in patients with pre-existing deficits.<sup>55</sup> This pharmacologic characteristic has been utilized as a rationale to design ART regimens including ZDV for patients with cognitive impairment, which is major clinical concern even in the modern ART era.<sup>55</sup> ZDV also penetrates into semen and cervicovaginal fluid nearly 2 to 3 fold more in these compartments in comparison with plasma; again the ratio changes significantly over the dose interval as above.<sup>56,57</sup> This may be an important pharmacologic consideration for

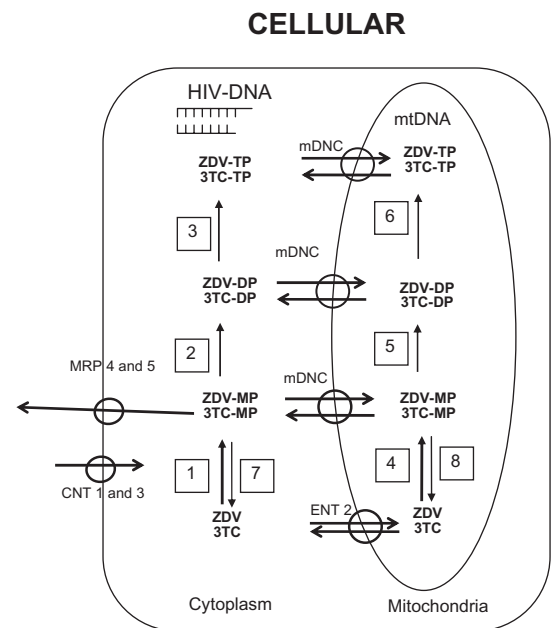
designing pre- or post exposure prophylaxis regimens in the future. ZDV is known to cross the placenta in pregnancy and penetrates breast milk, but breast milk concentrations are not high enough to elicit measurable concentrations in the feeding infant.<sup>58</sup>

The bioavailability of 3TC is about 85%.<sup>8</sup> Absorption is rapid with peak concentrations occurring in about 1 hour. Food delays, but does not significantly lower the extent of absorption. 3TC is mainly eliminated as unchanged drug in the urine. One minor metabolite for 3TC has been identified, a trans-sulfoxide, which accounts for about 5% of 3TC clearance. Significant dose adjustments are warranted for renal impairment, but not hepatic impairment.<sup>52</sup> 3TC exhibits two- or three-compartment pharmacokinetics with a terminal half-life in a typical dosing interval of approximately 6 hours.<sup>59</sup> Some references list a 1–3 hour half-life for 3TC, which probably represents the distribution phase. Other studies that measured 3TC out 48 hours after dosing observed a half-life of approximately 12 hours, which may represent a slowly equilibrating tissue. 3TC concentrations in CSF are approximately 5 to 10% those in plasma, which is considered moderate CSF penetration.<sup>55,59</sup> 3TC accumulates in semen by approximately 7-fold and in cervicovaginal fluid by approximately 4-fold compared with 3TC in plasma.<sup>57,60</sup> As mentioned for ZDV, these characteristics are potentially favorable for using 3TC in patients with cognitive dysfunction and for the prevention of sexual transmission of HIV. 3TC also crosses the placenta in pregnancy and penetrates breast milk.<sup>59</sup> In utero and breast milk concentrations of 3TC elicit measurable concentrations in the feeding infant, which may be relevant for HIV prophylaxis during breastfeeding or the development of drug resistance should the infant become HIV-infected.<sup>58,61</sup>

Like ZDV, there are few drug-drug interaction concerns with 3TC. It too has potential antagonistic phosphorylation issues with other deoxycytidine analogs such as with emtricitabine and the investigational agent, apricitabine.<sup>62</sup> Trimethoprim can reduce the renal clearance of lamivudine, but no dose change is recommended.<sup>8,63</sup>

### Intracellular profiles

The pharmacologically active form of ZDV and 3TC is the intracellular triphosphate anabolite. As shown in Figure 2, human kinases catalyze the phosphorylation



**Figure 2.** (1) thymidine kinase I (ZDV) and deoxycytidine kinase (3TC); (2) thymidylate kinase (ZDV) uridylate/cytidylate kinase (3TC); (3) nucleotide diphosphate kinase or 3' phosphoglycerate kinase; (4) thymidine kinase 2 (ZDV); (5) deoxyribonucleoside monophosphate kinases; (6) nucleoside diphosphate kinase H4; (7) cytosolic 5'-nucleotidase; (8) mitochondrial 5'-nucleotidase.

**Abbreviations:** MRP, Multidrug resistance protein; CNT, concentrative nucleoside transporter; mDNC, mitochondrial deoxyribonucleotide carrier; ENT, equilibrative nucleoside transporter.

of the drugs (not viral enzymes); thymidine kinase 1 (and TK 2 in resting cells), and thymidylate kinase convert ZDV to ZDV-MP and ZDV-DP.<sup>64</sup> Deoxycytidine kinase and uridylate/cytidylate kinase convert 3TC to 3TC-MP and 3TC-DP.<sup>65</sup> Nucleoside diphosphate kinase and 3'phosphoglycerate kinase converts ZDV-DP to the triphosphate form and 3'phosphoglycerate kinase converts 3TC-DP to the triphosphate form.<sup>66</sup> The main de-phosphorylation enzymes are 5' nucleotidases, which oppose the first phosphorylation step and convert monophosphates back to the parent drug.<sup>67</sup> Phosphatases are broad-spectrum dephosphorylation enzymes that can also dephosphorylate drug-phosphates to the parent drug.<sup>68</sup> It is not clear how the balance of these enzymes contribute to the intracellular profiles of NRTI-phosphates in vivo. The intracellular triphosphates are effectively trapped in the cell, at the site of action, due to the ionic phosphate groups. This is a unique and elegant pharmacologic characteristic of the NRTI class, and it also allows for studies of intracellular pharmacology in vivo.



In peripheral blood mononuclear cells (PBMCs) from patients taking ZDV and 3TC, typical intracellular triphosphate concentrations range from about 30 to 150 fmol/million cells for ZDV-TP and 3000 to 12000 fmol/million cells for 3TC-TP.<sup>61,69–71</sup> The half-life of ZDV-TP is about 7 hours and that for 3TC-TP is about 22 hours.<sup>69</sup> These half-lives for the pharmacologically active moieties are several-fold longer than the parent drug in plasma, and form the pharmacokinetic rationale for the dosing frequencies used in patients today (twice daily for ZDV and once-or twice-daily for 3TC). This later point bears special importance and need for reflection. The original dosing of ZDV was 250 mg 6 times daily (1500 mg/day) based on the 1 hour plasma half-life and the desire to maintain plasma concentrations near the in vitro  $EC_{50}$ .<sup>72</sup> Because significant ZDV toxicity was recognized over the ensuing years (anemia/neutropenia, myopathy, headache, nausea), doses were methodologically de-escalated to the present dose of 300 mg twice daily. A better understanding of the 7 hour intracellular half life of ZDV-TP in vivo at the beginning of ZDV's history would have enabled a more rational dosing strategy from the start. A similar but less dramatic story has unraveled for 3TC. As the long intracellular half-life of 3TC-TP became clear (>20 hours), the pharmacologic basis was established for once-daily dosing.<sup>73</sup> Once daily 3TC is the current standard of care for 3TC combinations with other once-daily NRTIs (such as abacavir or TDF). However, studies of ZDV-TP pharmacokinetics and pharmacodynamics do not support once-daily ZDV; thus ZDV-3TC combinations should remain twice daily at this time.<sup>16,74</sup> Plasma and intracellular characteristics for ZDV and 3TC are shown in Table 1.<sup>8,51,69</sup>

Patient factors that influence the intracellular triphosphate profiles for these drugs are largely unknown, although some in vitro information may give hints to potentially important factors in vivo.<sup>75</sup>

First, possible genetic variability in the enzymes responsible for governing NRTI-TP such as deoxycytidine kinase, may be a source of variability for intracellular pharmacology.<sup>76</sup> Second, differences in the regulation and expression of the kinases that phosphorylate these drugs may influence the intracellular profiles in vivo.<sup>39</sup> The regulation of thymidine kinase I, the enzyme that converts ZDV to ZDV-MP is a good example of a highly regulated enzyme. Its expression is dependent on the cell cycle with high expression during the S phase and cellular activation.<sup>77</sup> As an example, the phosphorylation of ZDV to ZDV-TP is over 100-fold greater in PBMCs stimulated with phytohemagglutinin (PHA) compared with resting cells.<sup>78</sup> Deoxycytidine kinase, on the other hand, is expressed during all phases of the cell cycle and the phosphorylation of 3TC to 3TC-TP proceeds nearly as well in resting cells as in PHA stimulated cells.<sup>78</sup> For these reasons, ZDV is referred to as a cell-activation-dependent NRTI and 3TC is a cell-activation-independent NRTI. How these in vitro findings translate to the in vivo setting is not entirely clear, but one can speculate that individuals with high levels of cellular activation, such as with increased serum levels of the mitogen, lipopolysaccharide may experience higher ZDV phosphorylation and toxicity.<sup>75,77,79</sup> Evidence of higher ZDV toxicity in individuals with advanced HIV has long been recognized, but the pharmacologic basis for this heightened sensitivity has not been elucidated.<sup>80</sup>

Some evidence suggests that gender is predictive of intracellular ZDV and 3TC. One study found about 2.3-fold and 1.6 fold higher intracellular ZDV-TP and 3TC-TP levels respectively, in 4 women compared with 29 men despite similar plasma concentrations ( $P < 0.01$ ).<sup>69</sup> Another study also found higher ZDV phosphates (MP plus DP plus TP) among 5 women versus 16 men (1.4-fold;  $P < 0.01$ ), and a third study found higher 3TC-TP in female compared with

**Table 1.** Typical pharmacokinetic characteristics in HIV-infected adults.

	Plasma ZDV	Plasma 3TC	Intracellular ZDV-TP	Intracellular 3TC-TP
Half-life	1 hr	6 hr	7 hr	22 hr
Steady-state concentrations	190 ng/mL	510 ng/mL	50 fmol/10 <sup>6</sup> cells	8500 fmol/10 <sup>6</sup> cells



male infants despite similar plasma concentrations (1.8-fold;  $P = 0.04$ ).<sup>61,81</sup> However, a separate study found lower ZDV-triphosphates in female compared with male adults although plasma concentrations were similar.<sup>82</sup> An *in vitro* study evaluated the effects of progesterone, estrogen, and testosterone on conversion of ZDV and 3TC to ZDV-TP and 3TC-TP in PBMCs and found no major effects, but some minor lowering on 3TC-TP for progesterone and testosterone (all differences were below 50% versus control).<sup>83</sup> Given that numerous studies suggest that women suffer more serious adverse events to NRTIs compared with men, additional research is warranted to assess sex differences in intracellular pharmacology.<sup>84</sup>

Other factors that could impact intracellular pharmacology include regulation, expression, and/or genetic variability in drug uptake and/or efflux transporters. *In vitro* studies suggest ZDV and 3TC are substrates for multiple transporters including the OATs, Multidrug Resistance Protein 4 and 5, P-glycoprotein, Breast Cancer Resistance Protein, and CNT—ENT.<sup>85–89,104</sup> Table 2 summarizes drug transporters that have been associated with ZDV and 3TC in non-human studies. However, few *in vivo* data are available to help put these *in vitro* data into clinical context. Additionally, it should be noted that early studies suggested that ZDV passed through cell membranes by simple diffusion.<sup>90</sup> One retrospective pilot study of ZDV-3TC-indinavir in HIV-infected patients has reported associations between polymorphisms in

MRP4 and intracellular 3TC-TP and ZDV-TP levels.<sup>91</sup> Further studies will be needed to confirm and extend these findings. In summary, the area of transporter pharmacology promises to enhance our understanding of ZDV-3TC disposition in humans, but it is currently unclear how the numerous *in vitro* findings extrapolate to the *in vivo* setting.

## Clinical Trial Experience

### Antiretroviral naïve adults

ZDV-3TC enjoyed several years as the nucleoside analog backbone of first choice for initial treatment of HIV.<sup>5</sup> Multiple large randomized controlled trials established the safety, efficacy, and durability of these agents in three-drug combinations among antiretroviral naïve patients.<sup>2–4</sup> An exception was the inferiority of three drug regimens consisting of all NRTIs such as ZDV-3TC-abacavir (ABC), which are less effective than ZDV-3TC with efavirenz.<sup>2</sup> However, ZDV-3TC-ABC, which is available as a co-formulation in a single tablet, is more efficacious than other triple NRTI regimens such as, TDF-3TC-ddI and TDF-3TC-ABC.<sup>92,93</sup> Nevertheless, ZDV-3TC-ABC should not be used unless no other preferred or alternate three-drug alternatives are available such as in cases of significant potential for major drug-drug interactions.<sup>5</sup> Among the clinical trials, ZDV-3TC-efavirenz emerged as a particularly effective and generally well-tolerated regimen compared with single protease inhibitor-based therapy (nelfinavir) and regimens

**Table 2.** Summary of transporters that might influence ZDV and 3TC disposition Oatp2, organic anion transporting polypeptide 2.

Example drug transporters associated with ZDV/3TC <i>in vitro</i>		
Location	Uptake	Efflux
Blood-cells	CNT 1 CNT 3	MRP 4 MRP 5
Cytoplasm-mitochondria	ENT 2 mDNC	ENT 2 mDNC
Blood-brain	OAT 1 OAT 3 Oatp2, like (3TC into CSF)	MRP 1, MRP 2, MRP 4, MRP 5, P-gp, BCRP
Kidney/Liver/Intestine	OAT 1, OAT 2, OAT 3	MRP 1, MRP 2, MRP 4, MRP 5, P-gp, BCRP

**Abbreviations:** MRP, Multidrug resistance protein; CNT, concentrative nucleoside transporter; mDNC, mitochondrial deoxyribonucleotide carrier; ENT, equilibrative nucleoside transporter; BCRP, breast cancer resistance protein; OAT, organic anion transporter; P-gp, P-glycoprotein; ENT, equilibrative nucleoside transporter; mDNC, mitochondrial deoxyribonucleotide carrier.



with d4T-ddI as NRTI backbones.<sup>2,3</sup> ZDV-3TC was shown to have a wider margin of safety compared with d4T-ddI in terms of mitochondrial toxicities such as peripheral neuropathy.<sup>3</sup>

More recently, several clinical trials have compared ZDV-3TC, which are dosed twice daily, to TDF-FTC or ABC-3TC, which are dosed once daily. The Gilead 934 study was an open-labeled randomized trial that compared TDF-FTC to ZDV-3TC both in combination efavirenz in antiretroviral naïve patients. After 48 weeks, 80% versus 70% of persons experienced undetectable HIV-RNA (<50 cpm) among those randomized to TDF-FTC versus ZDV-3TC respectively ( $P = 0.02$ ).<sup>7</sup> About twice as many persons randomized to ZDV-3TC discontinued therapy because of adverse events compared with TDF-FTC ( $P = 0.02$ ). The most common adverse event leading to study discontinuation for ZDV-3TC was anemia (14 subjects for ZDV-3TC versus 0 for TDF-FTC). ZDV-3TC was also associated with higher increases in total cholesterol and more loss of limb fat compared with TDF-FTC. The main safety concern for TDF-FTC is renal toxicity (proximal tubule impairment with loss of glucose and phosphorous) and resulting bone demineralization.<sup>94</sup> However, the 934 study suggested only slight reductions in glomerular filtration rate in those randomized to TDF-FTC compared with ZDV-3TC with no cases of serious renal impairment. Additional studies continue to show that serious renal impairment with TDF-FTC is rare.<sup>95</sup> ZDV-3TC was also compared with ABC-3TC both with efavirenz in 649 antiretroviral naïve adults.<sup>6</sup> At 48 weeks, similar proportions (~70%) of subjects in both groups experienced HIV-RNA < 50 cpm, but subjects randomized to abacavir achieved higher CD4 responses during the trial. This could be attributed to the general bone marrow suppressive effects of ZDV.<sup>5</sup> Subjects in the ZDV-3TC group also experienced more nausea, vomiting, and fatigue. These studies established the favorable safety and tolerability of TDF-FTC and ABC-3TC against the standard of ZDV-3TC. However, in resource limited settings where ZDV and d4T are combined with 3TC and nevirapine in inexpensive coformulations, ZDV-3TC is preferred over d4T-3TC because of a much wider safety margin in terms of lactic acidosis, peripheral neuropathy, and lipatrophy.<sup>5,96</sup>

## Selected special populations

ZDV-3TC is a standard of care for preventing mother to child transmission of HIV.<sup>9</sup> A pivotal placebo-controlled study of ZDV monotherapy to prevent mother to child transmission in 1994 showed a 70% reduction in HIV transmission for ZDV versus placebo.<sup>97</sup> Since that time, ZDV and ZDV-3TC have been used prominently in mothers and infants born to HIV-infected mothers as prophylaxis of HIV. Whenever possible, ZDV-3TC is the recommended NRTI backbone in pregnant women.<sup>9</sup> In resource limited settings, single dose nevirapine is sometimes used to prevent HIV transmission to infants. Unfortunately, this inexpensive and simple strategy is associated with up to 60% incidence of nevirapine resistance in a region where nevirapine is a first-line component of ART. ZDV-3TC has been used for short periods such as 4 or 7 days in the setting of single-dose nevirapine to inhibit viral replication during nevirapine elimination thus lowering the probability of selection of nevirapine resistant strains. Such a strategy has reduced the development of nevirapine resistance from approximately 60% to 7%.<sup>98</sup> Finally, extensive clinical experience exists for using ZDV-3TC in children and this NRTI backbone continues to be advocated in this population.<sup>10</sup>

## Drug resistance

Like any antiviral drug, resistance develops to ZDV and 3TC if replication continues in the presence of drug concentrations that exert selective pressure on the virus. ZDV has a relatively high genetic barrier to resistance in that two to three thymidine analog resistance mutations are generally needed to confer high-level resistance. 3TC on the other hand has a low genetic barrier to resistance in that a single mutation (the M184V) confers 100 to 1000-fold resistance to 3TC.<sup>99</sup> A unique feature of ZDV and 3TC is the interplay of selective pressures for resistance where the presence of the M184V mutation re-sensitizes ZDV resistant viruses to ZDV.<sup>99</sup> Similarly, some evidence suggests that ZDV exerts selective pressure to prevent the emergence of the K65R mutation which confers resistance to TDF.<sup>100</sup> This would provide a rationale to include ZDV in regimens with TDF simply to prevent the future development of K65R.<sup>101</sup> Taken together,





these observations provide a rationale to further study the use of ZDV as a resistance modulator in combination with other antiretroviral drugs.<sup>102</sup>

### Safety

3TC is a well-tolerated drug.<sup>5</sup> The main side effects in adults are headache and nausea, which are mild. All NRTIs have been associated with lactic acidosis, although the incidence is rare. One concern with 3TC is among hepatitis B co-infected patients who begin 3TC-containing ART and must stop therapy for some reason. Cases of severe hepatic flares have ensued

after ART discontinuations probably because of the removal of hepatitis B activity with 3TC.<sup>8</sup>

Tolerability issues have hampered the use of ZDV. The main tolerability issues are nausea/vomiting, headache, fatigue, and lipoatrophy, although the risk of lipoatrophy is not as high as with d4T.<sup>6,7</sup> Patients usually become tolerant of the gastrointestinal and fatigue side effects, and they are readily reversible upon drug discontinuation. Unfortunately, lipoatrophy is more difficult to reverse. Muscle toxicity was a side effect when ZDV was used at higher doses (up to 1500 mg/day), but is much rarer with the doses

**Table 3.** Summary of favorable and unfavorable characteristics of ZDV and 3TC for HIV.

	<b>Favorable</b>	<b>Ref</b>	<b>Unfavorable</b>	<b>Ref</b>
<b>ZDV</b>	Good CNS penetration/activity	55	Nausea, fatigue, anemia/neutropenia, lipoatrophy	6, 7
	Proven prevention of mother-to-child transmission	9	Unknown risk for mitochondrial or cellular toxicity emerging later in life	103
	Possible prevention of K65R mutation	101	Potentially lower potency versus other NRTIs	16
	Extensive clinical experience showing generally favorable long-term toxicity profile	5, 43	Extensive cross resistance with accumulating mutations	99
	High phosphorylation in activated cells	78	Possible additive bone marrow toxicity with drugs such as ribavirin and ganciclovir	5
	Clear dose recommendations for renal and hepatic dysfunction	8, 53	Low phosphorylation in resting cells	78
<b>3TC</b>	Well-tolerated and safe	5	M184V confers high level resistance to 3TC	99
	The M184V mutation sensitizes the virus to ZDV and other NRTI	99	Potential for hepatic flares upon discontinuation in hepatitis B coinfecting patients	8
	Active against hepatitis B	8	Unknown risk for mitochondrial or cellular toxicity emerging later in life	103
	Clear dose recommendations for renal and hepatic dysfunction	8, 63		
	Few drug-drug interactions	5		
	Extensive clinical experience showing favorable long-term toxicity profile	5		
	Equally-well phosphorylated in activated and resting cells	78		



used today. Anemia/neutropenia continue to be a concern and are more common in patients with advanced HIV.<sup>7</sup> Anemia/neutropenia are reversible upon drug discontinuation.

## Place in therapy

Table 3 summarizes the favorable and unfavorable characteristics associated with ZDV-3TC. These agents are long-standing NRTIs with extensive clinical experience in a wide spectrum of patients from in utero through childhood and adult ages. ZDV-3TC is currently a viable alternative NRTI backbone for initial therapy of HIV infection, among patients who should not use TDF-FTC because of relative or absolute contraindications such as renal insufficiency.<sup>5</sup> ZDV-3TC continue to be good choices for children and pregnant women and in resource limited settings where other more highly recommended options are not affordable.<sup>9,10,96</sup> The good CNS-penetration of this combination also makes it attractive for use in patients with HIV-associated neurologic deficits.<sup>55</sup> In the future, ZDV may be used in combination with other NRTIs such as TDF to prevent the K65R mutation, but this is only a research strategy at the present time. For about 20 years, ZDV and 3TC have endured as recommended NRTIs for HIV infection. This longevity of experience provides a basis for their continued usefulness today.

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