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Combination Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors

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Abstract

Introduction—The combination of two nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) and a third agent from another antiretroviral class is currently recommended for initial antiretroviral therapy. In general, N(t)RTIs remain relevant in subsequent regimens. There are currently six nucleoside reverse transcriptase inhibitors and one nucleotide reverse transcriptase inhibitor drug entities available, and several formulations that include two or more N(t)RTIs in a fixed dose combination. These entities have heterogeneous pharmacological and clinical properties. Accordingly, toxicity, pill burden, dosing frequency, potential drug-drug interaction, pre-existing antiretroviral drug resistance, and co-morbid conditions should be considered when constructing a regimen. This approach is critical in order to optimize virologic efficacy and clinical outcomes.

Areas covered—In this article, we review N(t)RTI combinations used in the treatment of HIV-infected adults. The pharmacological properties of each N(t)RTI, and the clinical trials which have influenced treatment guidelines are discussed.

Expert Opinion—It is likely that N(t)RTIs will continue to dominate the global landscape of HIV treatment and prevention, despite emerging interest in N(t)RTI-free combination therapy. Clinical domains where only few alternatives to N(t)RTIs exist include treatment of HIV/HBV co-infection and HIV-2. There is a need for novel N(t)RTIs with enhanced safety and resistance profiles compared to current N(t)RTIs.

Keywords

Antiretroviral therapy; nucleoside reverse transcriptase inhibitors; nucleotide reverse transcriptase inhibitor; HIV

1.0 Introduction

Zidovudine (ZDV), the first drug approved by the Food and Drug Administration (FDA) for Human Immunodeficiency Virus (HIV) treatment, became available in 1987. Between 1987 and 1995, despite approval of more agents for HIV treatment, monotherapy or dual therapy remained standard practice. Combination antiretroviral therapy (cART) with three antiretroviral agents became the standard of care in 1996. This revolutionized the management of HIV infection, resulting in substantial reduction in progression to acquired immunodeficiency syndrome (AIDS), opportunistic infections, hospitalization and death¹.

The combination of two nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) and a third agent from another antiretroviral class is currently recommended for initial cART^{2–4}. The third agent may be a non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), integrase strand transfer inhibitor (INSTIs) or a CCR5 receptor antagonist, depending on the clinical scenario and available resources. In general, N(t)RTIs

are an important component of first-line cART and typically remain relevant in subsequent regimens.

There are currently six nucleoside reverse transcriptase inhibitors (NRTIs) and one nucleotide reverse transcriptase inhibitor (NtRTI) drug entities, and several formulations that include two or more N(t)RTIs in a fixed dose combination. These entities have heterogeneous pharmacological and clinical properties. Accordingly, toxicity, pill burden, dosing frequency, drug-drug interaction potential, pre-existing antiretroviral drug resistance, and co-morbid conditions should be considered when constructing a regimen. This approach is critical in order to optimize virologic efficacy and clinical outcomes.

In this article, we review current N(t)RTI combinations used in the treatment of HIV-infected adults.

2.0 Mechanism of Action of N(t)RTIs

HIV is a single-stranded RNA genome, which is copied into double-stranded DNA by the enzyme reverse transcriptase. The N(t)RTIs compete with the naturally occurring deoxynucleosides - thymidine, adenosine, cytidine and guanosine – for incorporation into the elongating double-stranded DNA chain. By doing so, N(t)RTIs block the action of reverse transcriptase thus preventing further synthesis of viral DNA, resulting in inhibition of HIV replication. The N(t)RTIs are administered as prodrugs and must undergo intracellular phosphorylation to their active forms. The NRTIs, zidovudine (ZDV), lamivudine (3TC), didanosine (ddI), abacavir (ABV) and stavudine (d4T) are all active intracellularly in their triphosphate form. In contrast, tenofovir disoproxil fumarate (TDF), an NtRTI, is active as a diphosphate. Because of the intracellular activation of N(t)RTIs, the intracellular pharmacology of the drugs, such as half-life, are thought to be the clinically relevant parameters. N(t)RTIs also inhibit human DNA polymerases to varying degrees, which explains their different propensities for associated mitochondrial toxicities^{5,6}. Like other antiretroviral drugs, penetration of NRTIs into relatively protected anatomic compartments is variable, and possibly affects antiviral efficacy. The central nervous system penetration-effectiveness (CPE) score quantitatively estimates this variable for the central nervous system (CNS)⁷. Although CPE scores correlate with CNS HIV viral load, there has been less consistency between these scores and neuropsychological outcomes^{8,9}.

3.0 Pharmacology Overview of N(t)RTI

3.0.1 Zidovudine

Zidovudine is a thymidine analogue and was the first antiretroviral approved by the United States Food and Drug Administration (FDA) for the treatment of HIV infection in 1987. It is currently the only reverse transcriptase inhibitor that is available in both an oral and intravenous form. Standard dosing of all N(t)RTIs can be found in Table 1. Following oral administration, ZDV is rapidly absorbed, reaching maximum concentrations within 1.5 hours, and has a bioavailability of $64(\pm 10)\%$ ⁶. The plasma exposure of ZDV throughout the dosing interval, or area under the curve (AUC), is similar when it is administered with or without food. Following absorption, ZDV is well-distributed throughout the body, represented by a volume of distribution (Vd) of 1.6 L/kg and relatively low plasma protein binding of less than 38%¹⁰. These pharmacokinetic characteristics result in a high central nervous system penetration-effectiveness (CPE) score^{7,11,12} and efficient transfer of the drug into the placenta, demonstrated by a median cord blood to plasma concentration ratio of 1.85 (range 0.17–3.66)^{13,14}.

The predominant pathway for ZDV metabolism is glucuronidation in the liver, kidney, and intestinal mucosa. Excretion is mainly renal, via glomerular filtration and active tubular secretion, with 14% of the parent compound and 74% of the glucuronide recovered in urine after oral administration in healthy subjects⁵. Compared to other N(t)RTIs, ZDV has a short intracellular half-life, approximately 3–4 hours, necessitating multiple daily dosing¹⁵. In patients with severe renal impairment, clearance of ZDV is reduced approximately 50%, thus a dose adjustment is required when the estimated creatinine clearance (CrCl) is less than 15 ml/min (Table 1)^{16,17}.

3.0.2 Didanosine

Didanosine is a purine analogue, which was approved for the treatment of HIV in 1991. This drug is easily degraded by stomach acid hence is usually administered in adults as the enteric-coated formulation, which does not dissolve until it reaches the small intestine where absorption occurs. Didanosine is also available as a powder formulation buffered with antacids to protect the drug from degradation in the stomach. Another buffered formulation of ddI (chewable/dispersible tablets) was discontinued in the US in 2006, but is still available in other parts of the world. After oral administration, the overall bioavailability of ddI is approximately 42(±8) %, although the time to maximum absorption depends on the formulation, ranging from less than 1 hour for the chewable tablets to 2.3 hours for the enteric-coated capsules¹⁸. Binding of didanosine to plasma protein is low (<5%), contributing to its ability to cross the placenta¹³. However, the central nervous system (CNS) penetration is approximately 20% and it has a low CPE score⁷.

The dosing of ddI is weight dependent and it requires dosage adjustment in persons with renal insufficiency (Table 1). Approximately 41–69% of the dose is recovered unchanged in the urine within eight hours after administration¹⁹. The intracellular half-life of ddI triphosphate is up to 40 hours, supporting once daily administration²⁰. No dosage adjustment is recommended in persons with liver disease.

3.0.3 Stavudine

Stavudine is also a thymidine analogue and was approved for the treatment of HIV in 1994. After oral administration, d4T is thoroughly and quickly absorbed, with a bioavailability of 86(±18) % and a maximum concentration achieved within one hour. The absorption of d4T is not impacted by co-administration with food, so d4T may be administered without regard to meals¹⁰. Stavudine is negligibly bound to proteins, hence is well distributed throughout the body and freely crosses the placenta through passive diffusion^{13,21}. Stavudine has an intermediate CPE score⁷. Its intracellular half-life has been estimated to be between 3.5 hours (in vitro) and 7 hours (in vivo)^{21,22}. Stavudine is primarily excreted unchanged in the urine (95% recovered in urine, mostly unchanged drug), therefore a dosage adjustment is required in patients with renal impairment (See Table 1)²¹. No dosage adjustment is required in persons with hepatic insufficiency.

In recent years, d4T use has become rare in developed countries and is even being phased out in resource-limited settings because of concerns about long-term cumulative toxicity⁴. Stavudine dose recommendations in the United States are based on patient weight and it is advised to decrease the dose with the occurrence of adverse effects. However, the World Health Organization (WHO) has advised against use of 40 mg twice daily since 2006²³, although this dose is still listed in the US prescribing information for patients > 60kg. Internationally, 30 mg twice daily has become the standard initial dose for all adult patients (Table 1 is based on this WHO recommendation), however both doses have been associated with toxicities²⁴. As such, there is no consensus on the optimal dosage of d4T; even lower

doses than 30 mg twice daily are being evaluated to improve long-term tolerability while preserving efficacy.

3.0.4 Lamivudine

Lamivudine, a negative enantiomer of a cytidine analogue, was approved for HIV treatment in 1995. Following oral administration, it is well absorbed (bioavailability of 86%) and reaches its maximum concentration within 1.5 hours²⁵. Though the time to and resultant maximum concentration is impacted by the administration of food, the AUC of 3TC is not impacted; therefore 3TC can be administered without regard to meals. Lamivudine is not extensively bound to protein (<36%) and is well distributed throughout the body (volume of distribution = 1.3L/kg)²⁶, resulting in extensive distribution of 3TC between maternal and fetal circulation²⁷. However the CSF penetration is very low (CSF: Serum ratio = 0.06), despite an intermediate CPE score^{7,28,29}.

Lamivudine has a long intracellular half-life, ranging from approximately 9 to 32 hours, permitting once or twice daily dosing^{25,30}. Similar to other NRTIs, 3TC is excreted mainly through the kidneys and requires dose adjustment during renal insufficiency (Table 1). Pharmacokinetic parameters are unchanged in patients with hepatic insufficiency; therefore 3TC does not require a dosage adjustment in this population²⁶.

3.0.5 Abacavir

Abacavir (ABV) sulfate is a structural analogue of guanine, approved for HIV treatment by the FDA in 2001. Following oral administration, ABV tablets are 83% bioavailable and reach the plasma maximum concentration between 0.6 to 2.5 hours^{31,32}. Administration with food impacts maximum concentrations achieved however there is no change in the AUC so ABV can be administered with or without food. Abacavir is well distributed in the body with a volume of distribution of 0.8 ± 0.15 L/kg and is about 50% protein bound³³. Studies indicate that ABV extensively distributes to the placenta by simple diffusion³⁴, and it has a high CPE score despite only 27–36% of the plasma concentration reaching the CSF^{7,31}.

Unlike most N(t)RTIs, the pharmacokinetics of ABV are not significantly impacted by renal insufficiency as only 1% of the drug is found unchanged in the urine. The drug is primarily metabolized in the liver by alcohol dehydrogenase and uridine diphosphate to two inactive metabolites which are eliminated through the kidneys³². The estimated intracellular half-life is variable, ranging from 4.8 to 39 hours in one study³⁵. Regardless, the average intracellular half-life (14.1 hours)³⁵ is long enough to support once or twice daily dosing. Abacavir should be used with caution, and at a reduced dose, in patients with mild liver disease (Child-Pugh score 5–6), but is contraindicated in the presence of moderate to severe impairment (Child-Pugh score >6)³³. It does not require dosage adjustment in the presence of renal insufficiency. (Table 1)

3.0.6 Tenofovir

Tenofovir is an adenosine analog, which was approved in 2001 by the FDA and remains the only available NtRTI for treatment of HIV. Unlike NRTIs that require conversion to the triphosphate for activation, TDF is active as a diphosphate making it active against dividing and non-dividing cells^{5,36}. Following oral administration in the fasted state, bioavailability of TDF is approximately 25%, and the maximum concentration is reached within an hour. Administration of TDF with high fat meal increases its bioavailability by approximately 40%, however a light meal does not significantly change its pharmacokinetic parameters. Despite this increase in bioavailability with high fat meal, TDF is approved for use with or without food³⁷. Tenofovir is well distributed throughout the body with minimal protein binding. Tenofovir effectively crosses the placental barrier as well as the blood-

cerebrospinal fluid barrier but has limited ability to cross the blood-brain barrier, and has low CPE ranking^{7,38,39}.

The intracellular half-life of TDF is estimated to be greater than 60 hours, allowing for once daily dosing⁴⁰. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Approximately 70–80% of the dose is recovered in the urine as unchanged drug within 72 hours of intravenous administration. Tenofovir has been associated with renal impairment, a dose related toxicity, therefore it is essential to monitor renal function and adjust TDF doses accordingly in persons with renal insufficiency. There is no dosage adjustment for liver disease³⁷.

3.0.7 Emtricitabine

Emtricitabine is a cytidine analog that was approved by the FDA for HIV treatment in 2003. The bioavailability of emtricitabine capsules is 93% following oral administration, however the solution is less bioavailable (75%) resulting in different dosing recommendations between the two formulations. The maximum concentration is reached within 1–2 hours, and the AUC of FTC is not affected by food, so either formulation can be taken with or without food. Emtricitabine is well distributed throughout the body and minimal protein binding⁴¹. Emtricitabine has an intermediate CPE score⁷.

Emtricitabine has a plasma half-life of 10 hours and an intracellular half-life about 39 hours, allowing for once daily dosing^{5,40}. Emtricitabine undergoes limited metabolism through hepatic oxidation and glucuronidation and is mainly excreted unchanged by the kidneys, therefore dosage adjustment is required in patients with renal impairment (Table 1).

3.1 Drug Interaction Considerations

N(t)RTIs are not substrates for, nor do they inhibit or induce, the cytochrome P450 enzyme system. Therefore, many of the interaction concerns which are common with other classes of antiretroviral agents are not a concern with N(t)RTIs. Some mechanisms of potential interactions with N(t)RTIs include competition for renal elimination pathways between concomitant medications and those N(t)RTIs that are exclusively eliminated via the kidneys, and changes to or alcohol dehydrogenase pathways which can influence the elimination of zidovudine and abacavir, respectively. Tenofovir has significant interactions to consider with concomitant antiretroviral therapy. Specifically, the dose of ddI must be reduced while atazanavir must be boosted with ritonavir if coadministered with tenofovir. It is advisable to consult an up to date, HIV-focused, drug interaction reference when selecting the antiretroviral regimen, giving consideration to the patient's concomitant medical conditions and medications.

4.0 Efficacy & Safety of combination N(t)RTIs

4.1 Zidovudine/Lamivudine

Zidovudine was the first antiretroviral agent used in clinical trials. In early placebo-controlled studies, dramatic but short-lived improvement was observed with ZDV monotherapy. In a placebo controlled study of 282 patients reported by Fischl et al in 1987, the use of ZDV was associated with a four- to six-fold reduction in mortality at nine months compared to placebo⁴². The study was stopped prematurely due to excess mortality in the placebo group. Early experience with 3TC monotherapy demonstrated extremely rapid emergence of 3TC resistance^{43,44}. Based on in-vitro studies that showed the addition of 3TC to ZDV delayed resistance to ZDV, dual therapy was investigated⁴⁵. Combination therapy with ZDV/3TC was not common until clinical trials showed improved virologic suppression and improvement in CD4⁺ T cell count compared to NRTI monotherapy^{46–49}. In 1997,

Combivir™ (ZDV 300 mg plus 3TC 150 mg, GlaxoSmithKline Ltd, Brentford Middlesex, UK), became the first fixed-dose drug combination for HIV treatment.

One of the early trials supporting the efficacy and safety of ZDV/3TC as part of cART was the AIDS Clinical Trial Group (ACTG) 384 study (Table 2). This was a multicenter study where 620 subjects were randomized to six treatment groups: ddI/d4T or ZDV/3TC given with efavirenz, nelfinavir or efavirenz and nelfinavir. Patients who received the combination of ZDV/3TC plus efavirenz showed a trend towards longer time to virologic failure, and a lower incidence of dose-modifying toxic effects including peripheral neuropathy⁵⁰.

Zidovudine has been associated with dose-related mitochondrial toxicity^{51,52}. Anemia from bone marrow suppression is also a major concern with ZDV use, particularly in middle and low income countries. A retrospective cohort study in India reported that 7.9 % of patients developed severe anemia (hemoglobin < 6.5 g/dL) while on ZDV⁵³. Among Africans, a 6.6% incidence of severe anemia was reported in the DART study⁵². Switching from ZDV has been shown to improve hematologic parameters. The Simplification With Easier Emtricitabine and Tenofovir (SWEET) study demonstrated reduced incidence of anemia and improved lipid parameters after switching from ZDV/3TC to TDF/FTC⁵⁴. Other studies have also demonstrated similar results^{55,56}. Preliminary evidence from Thailand suggests that treatment-limiting toxicity associated with ZDV can be reduced without compromising efficacy if administered at the reduced dose of 200 mg twice daily⁵⁷.

Despite these drawbacks, AZT/3TC remains a potent NRTI combination and an important component in HIV pharmacotherapy. It is currently the preferred NRTI combination for pregnant women in the US, and is a first-line NRTI combination in the 2010 WHO treatment guideline, although no longer considered a preferred agent in developed countries due to toxicity concerns^{58–61}.

4.2 Tenofovir/Emtricitabine

The GS903 study (Table 2), the first large placebo-controlled double-blind trial of TDF in antiretroviral-naïve patients, compared the safety and efficacy of once-daily TDF with twice-daily d4T, both given with twice-daily 3TC and once-daily efavirenz. In this study, TDF demonstrated non-inferiority to d4T at 96 and 144 weeks, with better lipid profiles and significantly less lipodystrophy than d4T⁶⁰.

The fixed dose combination of TDF/FTC has become the preferred NRTI combination in the US following the GS934 study^{59,61–63}. This was an open label non-inferiority trial comparing ZDV/3TC plus efavirenz to TDF/FTC plus efavirenz. A significantly greater number of patients on TDF/FTC plus efavirenz achieved HIV-1 RNA < 50 copies/mL at 48 weeks, and the trend was maintained at 144 weeks^{61,64,65}. The combination of TDF/FTC plus efavirenz was also better tolerated than ZDV/3TC plus efavirenz with significantly fewer treatment-limiting adverse events in the TDF/FTC arm⁶⁵. K65R, the mutation that confers resistance to TDF did not emerge in any of the virologic failures in GS934. Notably, the K65R mutation can emerge following exposure of non-B subtype HIV-1 to some other reverse transcriptase inhibitors (RTIs) especially d4T^{66,67}.

Tenofovir and FTC have demonstrated a favorable safety profile in clinical trials. Most reported adverse effects such as gastrointestinal events^{60,68,69} for TDF and headache for FTC are rarely clinically significant. Palmer hyperpigmentation, which can be mistaken for secondary syphilis, has been reported in patients treated with emtricitabine^{70–72}. As with other N(t)RTIs, lactic acidosis is considered a potential risk with TDF and FTC, however this has been rarely reported^{70–72}.

One concern has been the association of TDF with renal toxicity², although clinically significant changes in renal function rarely occur in patients with normal baseline renal function^{61,71}. In large clinical trials and cohort studies, TDF has been associated with renal toxicity in approximately 0.5% of patients^{73,74}. In one study, decrease in glomerular filtration rate (GFR) was more severe and proximal tubular dysfunction more frequent with TDF-based therapy⁷⁵. Tenofovir-related decrease in creatinine clearance⁷⁶ or tubular dysfunction⁷⁷ appear to correlate with high plasma concentration of the drug. The potential for renal adverse effects with TDF use appears to increase with duration of exposure, aging, presence of baseline renal impairment, or combination with some ritonavir (RTV)-boosted PIs⁷⁸. Accordingly, close monitoring of renal function is necessary, particular in patients with these risk factors. In addition, dose reduction of TDF in patients with renal insufficiency is recommended to minimize the risk of nephrotoxicity. The other concern associated with TDF is bone loss, reflected as decreased bone mineral density (BMD)^{79,80}. Considering all regimens evaluated to date, initiation of cART has invariably led to a decline in BMD. The magnitude of BMD decrease has, however, been 1–2% greater in subjects treated with TDF. This effect peaks at 24–48 weeks of therapy, remaining stable thereafter^{60,81,82}. Recent studies have shown an association between cumulative use of tenofovir and risk of bone fractures⁸³.

In the current US treatment guidelines⁵⁹, TDF/FTC is the only preferred N(t)RTI combination for treatment-naïve patients. This is owed to its efficacy, safety, and availability of two fixed dose combinations (Truvada™: TDF 300 mg and FTC 200 mg, and Atripla™: TDF 300 mg, FTC 200 mg and EFV 600 mg) allowing for ease of administration. The availability of generic TDF/3TC fixed dose combinations in resource-limited settings resulted in the combination becoming a recommended N(t)RTI option in the 2007 WHO treatment guidelines. In addition, co-formulated tenofovir plus emtricitabine is the preferred NRTI combination in HBV/HIV co-infected patients, though the individual drugs or tenofovir plus lamivudine may be used as well.

4.3 Abacavir/Lamivudine

Several large studies have compared the efficacy and safety of ABV to ZDV and TDF in antiretroviral-naïve patients. The CNA30024 study compared ABV/3TC to ZDV/3TC, both in combination with efavirenz, and found both combinations to be equally effective⁷¹. A second study (ACTG 5202) compared ABV/3TC to TDF/FTC, each in combination with efavirenz. In that study, patients were stratified based on baseline HIV-1 RNA ($\leq$ or $<$ 100,000 copies/mL) and virologic failure was defined as HIV-1 RNA $<$ 200 copies/mL. Interim analysis of the data showed that among persons with baseline HIV-1 RNA above 100,000 copies/mL, there was an excess virologic failure in the ABV/3TC arm (17%) compared to the TDF/FTC group (7%); hazard ratio: 2.33; $p = 0.0003$. There was also a shorter time to the first significant adverse event and treatment modification in the ABV/3TC group⁸⁴. In the HEAT trial sponsored by GlaxoSmithKline, however, ABV/3TC and ZDV/3TC (each combined with lopinavir/ritonavir) had comparable virologic efficacy, safety and tolerability, even in patients with baseline HIV-1 RNA $>$ 100,000 copies/mL⁷².

Abacavir hypersensitivity reaction is the most common severe adverse reaction in patients taking ABV, with a reported frequency of 2–10%^{70–72}. This reaction is strongly associated with HLA-B*5701^{70–72}, although cases have been described in persons without this genetic predisposition^{70–72}. Screening for HLA-B*5701 is recommended prior to treatment with ABV. Persons determined to be HLA-B*5701 positive have the greatest risk for hypersensitivity and should not be prescribed ABV^{2,85–87}. A meta-analysis of 34 studies showed relative protection against ABV hypersensitivity reaction in persons of African racial origin, male sex and more advanced HIV disease⁸⁸, which is consistent with the lower prevalence of HLA-B*5701 in this population⁸⁹. Use of ABV was associated with an

increased risk of coronary heart disease in the Data Collected on the Adverse Events of Anti-HIV Drugs (DAD) study⁹⁰. This was also observed in the Strategies for Management of Anti-Retroviral Therapy (SMART) study⁹¹. In the ANRS CO4 study, initiation of ABV was associated with an increased risk of myocardial infarction, but longer exposure was not⁹². However, in separate prospective, randomized studies sponsored by both GlaxoSmithKline and the ACTG, use of ABV was not associated with an increased risk of myocardial infarction^{93,94}.

Given these considerations, the US treatment guidelines no longer recommend ABV/3TC as a preferred N(t)RTI backbone in ART-naïve patients, although studies to date have not conclusively identified a mechanism to explain an association between ABV and increased cardiovascular risk^{70–72}. Notably, a recent meta-analysis (N= 9832) conducted by the FDA did not find increased risk of myocardial infarction in patients treated with ABV compared to other N(t)RTIs^{70–72}. Since renal insufficiency is an independent predictor of cardiovascular disease, perhaps preferential use of ABV over TDF in patients with renal insufficiency partly explains the earlier associations between ABV and cardiovascular disease⁹¹. Overall, ABV/3TC is appropriate for some patients, particularly those with contraindications or intolerance to TDF.

4.4 Stavudine/Lamivudine

The use of stavudine/lamivudine as part of cART was popularized by the 2NN study⁹⁵, an open label randomized trial which compared once daily nevirapine, twice daily nevirapine or efavirenz each in combination with d4T/3TC. A meta-analysis of nine randomized control studies with a total of 2,159 patients comparing efficacy of cART containing d4T to ZDV found no statistically significant difference, but was limited by suboptimal data quality⁹⁶. Stavudine also demonstrated comparable virologic efficacy as TDF in the 903 study, which compared TDF/3TC and efavirenz to d4T/3TC and efavirenz⁶⁰.

Despite the efficacy of this combination, a major factor limiting the use of d4T is its poor safety profile. Documented adverse effects of d4T continue to accumulate over time and include lipodystrophy (~19%), lactic acidosis (~1%) and peripheral neuropathy (5–15%)^{60,97,98}. This is consistent with in vitro evidence of substantial mitochondrial toxicity^{70–72}. Switching from d4T to TDF has been shown to improve systemic and peripheral fat mitochondria⁹⁹. Improvements in serum lipids and peripheral lipoatrophy have been described as well, the latter being modest in most cases^{70–72}. HIV treatment guidelines in the US and Europe no longer recommend the use of d4T^{2,59}, however this drug remains widely used in resource-limited settings¹⁰⁰. The WHO has called for countries to phase out d4T due to its side effects⁵⁹.

4.5 Didanosine plus other N(t)RTIs

Didanosine was evaluated in combination with 3TC or FTC in two trials of ART naïve patients, FTC-301 and GESIDA 3903^{101,102}. A larger trial (ACTG 5175) compared the efficacy and safety of 3 regimens (3TC/ZDV plus efavirenz, TDF/FTC plus efavirenz or ddI/3TC plus atazanavir)¹⁰³. In that study, the ddI/3TC plus atazanavir arm was discontinued due to the high probability of treatment failure defined as: HIV-1 RNA > 1,000 copies/ml from week 16, AIDS or death; HR 1.67 (CI 1.02, 2.75). Didanosine has also been associated with pancreatitis, peripheral neuropathy and non-cirrhotic portal hypertension^{104–106}, effects that are presumably related to mitochondrial toxicity¹⁰⁷.

Didanosine should not be used with d4T due to overlapping toxicities. There are limited data on the combination of ddI/ZDV or ddI/ABV as part of cART. In one of the few studies on the combination of ddI/ZDV, the TSHEPO study, 650 patients were randomized to ZDV/

3TC, ZDV/ddI or d4T/3TC; each with either nevirapine or efavirenz. After a median follow-up period of 104 weeks, 11% of patients in the ZDV/ddI group had virologic failure and drug resistance mutations compared to 2% in the other two groups. The frequencies of grade 3 or 4 adverse effects were however equally distributed among the three NRTI groups.

Co-administration of TDF and ddI has been associated with high rates of early virologic failure and emergence of resistance. In two studies, patients taking TDF/ddI with either efavirenz or nevirapine experienced higher rates of early virologic failure, compared to patients on 3TC/ddI with either efavirenz or nevirapine, particularly in patients with CD4 cell counts less than 200 cells/mm³ and HIV-1 RNA above 100,000 copies /ml at time of ART commencement^{108,109}. Pharmacokinetic studies have also shown that co-administration of TDF and ddI increases systemic exposure to ddI by 40–60%, thereby increasing the risk of ddI-related adverse effects¹¹⁰. The dose of ddI must be reduced when used in combination with TDF. Co-administration of TDF and ddI is not currently recommended. Due to the adverse event profile, which may limit efficacy, didanosine is not currently recommended as a first line drug for HIV treatment.

4.6 N(t)RTI only Combination Antiretroviral Therapy

4.6.1 Abacavir /Lamivudine/ Zidovudine—One of the early studies that investigated the use of NNRTI- and PI-sparing cART was the ACTG 5095¹¹¹. In this study, ABV/3TC/ZDV was compared to ZDV/3TC plus efavirenz and ABV/3TC/ZDV plus efavirenz. The primary end-point was virologic failure defined as HIV-1 RNA >200 copies/ml after week 16. In the ABV/3TC/ZDV group 21% had virologic failure compared 10% in the efavirenz groups. At week 48, 74% of patients randomized to ABV/3TC/ZDV and 89% in the efavirenz groups had HIV-1 RNA < 200 copies/ml. ABV/3TC/ZDV arm of the study was prematurely discontinued due to increased rate and time to virologic failure. The efficacy and safety of ABV/3TC/ZDV was compared to ZDV/3TC plus nevirapine in the DART trial (N=600)¹¹². After 48 weeks, 77% of patients in the nevirapine arm had HIV-1 RNA < 50 copies/ml compared to 62% in the ABV group (p < 0.001). Patients in the nevirapine arm however had a higher incidence of grade 4 safety events (36% vs. 24%) and death (5% vs. 3%).

The combination of ABV/3TC/ZDV has shown better results than some other N(t)RTI only combinations^{113,114}, and is considered an acceptable alternative in selected situations where NNRTIs, PIs, INSTIs, and CCR5-receptor antagonists are contraindicated or unavailable⁴. It is not recommended in the US HIV treatment guidelines⁵⁹.

4.6.2 Tenofovir/Abacavir/Lamivudine—Early trials of TDF/ABV as part of cART for HIV infection showed unacceptable high failure rates accompanied by rapid development of M184V and K65R mutations^{113,114}. Illustratively, in the ESS30009 study, 340 treatment-naïve patients were randomized to TDF/ABV/3TC or ABV/3TC plus efavirenz. Early virologic failure was documented in the TDF/ABV/3TC group, requiring modification of the study protocol. The TDF/ABV/3TC group also had a higher incidence of K65R and M184V mutations¹¹³. This combination is not recommended in treatment-naïve patients, but is occasionally considered in treatment-experienced patients with limited options.

4.6.3 Abacavir/Lamivudine or Emtricitabine/Zidovudine/Tenofovir—A few relatively small studies have evaluated quadruple-N(t)RTI regimen comprising ABV, 3TC or FTC, ZDV and TDF. In a single-arm efficacy study of 54 ART-naïve patients, 63% of patients had HIV-1 RNA less than 50 copies/ ml at week 96 in an intent-to-treat analysis¹¹⁵. Similarly in an open-label efficacy and safety study involving 9 subjects with HIV/Hepatitis B co-infection, 83% of subjects had HIV-1 RNA < 50 copies/ml at week 48¹¹⁶. In one of the

few large studies of quadruple-N(t)RTI, 322 ARV naïve patients were randomized to TDF/FTC/EFV (n=114), TDF/FTC/ritonavir-boosted atazanavir (n=105) or TDF/FTC/ABV/ZDV (n=103). The primary endpoint was time weighted mean change in HIV-RNA from baseline to week 48. Although non-inferiority for the primary endpoint was established, the combination of TDF/FTC/ABV/ZDV was less potent than TDF/FTC/EFV in superiority analysis¹¹⁷. In addition, serious adverse effects occurred more frequently in the quadruple-N(t)RTI arm.

4.7 N(t)RTIs after failure of first-line cART

The choice of drugs for second-line therapy should be guided by ART history, available treatment options and resistance pattern, where available. Where resistance testing is not feasible, a simple guide is to introduce drugs with non-overlapping resistance patterns to the failing N(t)RTIs and to which the patient is naïve⁴. For example, patients exposed to ZDV in first-line cART may be switched to a second-line regimen containing TDF and vice-versa. Optimal second-line cART should contain at least 2 or more new agents, the goal being presence of at least two fully active agents in the regimen^{4,59}. N(t)RTI combinations that are generally avoided in initial cART may be considered for second-line and subsequent therapy, provided the potential benefit outweighs potential risks.

The M184V mutation is common in patients failing cART containing 3TC or FTC¹¹⁸. This mutation causes high-level resistance to 3TC and FTC, but it reduces viral fitness and can increase susceptibility to ZDV, d4T and TDF. Accordingly, 3TC or FTC is often retained in the second-line cART despite evidence of the M184V mutation. This widespread practice is yet to be validated in a large prospective trial.

5.0 Expert Opinion and Conclusion

N(t)RTIs continue to dominate the global landscape of HIV treatment, triggered by the relatively early entry of NRTIs into the clinical and research arenas. Tenofovir, the only NtRTI, has solidified this frontline status particularly in developed countries. In RLS, N(t)RTIs are more available than PIs, INSTIs and CCR5 antagonists, however the most readily available N(t)RTIs are often 3TC and the thymidine analogues ZDV and d4T. Tenofovir and ABV are less often prescribed but use of TDF is increasing, driven by WHO guidelines which recommend its use in HIV/HBV co-infected persons and evidence that TDF is more cost-effective than d4T despite higher purchase cost of TDF⁴. Critically, N(t)RTIs are active against HIV-2. Although no consensus exists on optimal treatment of HIV-2, it is clear that N(t)RTIs should constitute an important component. HIV-2 is a distinct HIV lineage which accounts for up to one-third to one-half of prevalent HIV in endemic regions such as parts of West Africa¹¹⁹. Unlike HIV-1, HIV-2 is constitutively resistant to NNRTIs due to its unique amino acid conformation relative to NNRTI binding pocket as well as naturally occurring polymorphisms¹²⁰. Polymorphisms also render HIV-2 essentially resistant to some PIs, notably atazanavir¹²¹, but it remains susceptible to raltegravir (an INSTI) while R5-tropic strains are expected to be susceptible to maraviroc.

The importance of N(t)RTIs in HIV therapeutics has appropriately begun to extend into HIV prevention strategies (pre-exposure and post-exposure prophylaxis). Virtually all the trials demonstrating the effectiveness of antiretroviral prophylaxis have utilized TDF in oral or intravaginal gel formulations^{122,123} or oral TDF/FTC^{124,125}. Other potential prophylactic agents such as maraviroc are being explored, again typically in combination with N(t)RTIs.

Recently, coalescing concerns about long-term toxicity of some N(t)RTIs and transmitted drug resistance have stimulated interest in regimens that are free of N(t)RTIs and NNRTIs (i.e. reverse transcriptase inhibitor (RTI)-free cART). A variety of RTI-free regimens have

been evaluated with none demonstrating superiority over current RTI-based regimens^{126–128}. As such, no RTI-free regimen has gained widespread clinical approval, but this may change as more RTI-free regimens undergo clinical trials. Another approach aimed at achieving “nuc-free” ART entails discontinuation of N(t)RTIs in patients who have achieved viral suppression on an N(t)RTI-containing regimen. This concept showed promise in the MONET trial where patients with at least six months viral suppression on regimens containing a boosted PI or NNRTI plus two N(t)RTIs were switched to darunavir/ritonavir 800/100 mg daily monotherapy¹²⁹. Using intent-to-treat analysis at 48 weeks, 84% and 85% of patients maintained plasma HIV RNA < 50 copies/mL in the N(t)RTI-free and N(t)RTI-containing arms, respectively. Similar promising results were shown in MONOI-ANRS 136¹³⁰ but there has been limited uptake of this strategy in clinical practice, perhaps reflecting concerns that boosted PI monotherapy may be associated with early virologic failure and PI resistance⁵⁹.

Meanwhile, novel compounds are in development to address N(t)RTI toxicity and/or resistance concerns. Notable novel N(t)RTIs include GS-7340 (a TDF prodrug that is directly delivered to peripheral blood mononuclear cells as opposed to plasma, thus promising less toxicities)¹³¹. Development of apricitabine (an NRTI with activity against M184V bearing HIV strains and no known signature mutation)¹³² was recently put on hold pending a potential out-licensing agreement. Another compound in development is amdoxovir a guanosine analogue with synergistic antiviral activity with ZDV¹³³. Overall, since N(t)RTIs target a relatively conserved and critical enzyme in the viral life-cycle currently available safe and effective N(t)RTIs will continue to play vital roles in HIV therapy well into the foreseeable future. The role of currently investigational N(t)RTIs is less certain given the expanding list of antiretroviral agents from other classes that are safe and effective against NRTI-resistant HIV while avoiding NRTI toxicities.

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Article highlights

- N(t)RTIs are an important ART backbone in treatment naïve or treatment experienced patients
- N(t)RTIs have some class properties but also distinct pharmacologic, efficacy and toxicity profiles
- Co-formulated tenofovir plus emtricitabine is the preferred N(t)RTI combination in developed countries and its use is increasing in developing countries
- There are evolving concerns about long-term effects of some N(t)RTIs including TDF
- Triple or quadruple N(t)RTI regimens are inferior to NNRTI or boosted PI based regimens
- There is a need for novel N(t)RTIs that can overcome resistance to current N(t)RTIs and are safe long-term

Table 1
Summary of dosing and main adverse effects associated with nucleoside/nucleotide reverse transcriptase inhibitors *

Drug	Adult Dose	Dosage adjustment	Main adverse effects	Comments
Abacavir (ABV)	300 mg twice daily or 600 mg daily	<ul style="list-style-type: none"> No adjustment required for renal impairment Mild hepatic impairment (Child-Pugh 5–6): 200 mg every 12 hrs Moderate to severe hepatic impairment (Child-Pugh > 6), consider alternative therapy 	<ul style="list-style-type: none"> <i>Hypersensitivity Reaction:</i> At least two of the following symptoms - rash, fever, fatigue, GI symptoms, upper respiratory symptoms <i>Note:</i> symptoms typically worsen if ABV is continued 	<ul style="list-style-type: none"> If possible, screen for HLA-B 5701. If positive, patient should <u>NOT</u> receive ABV and should have ABV allergy documented in their chart. Typically occurs within first 6 weeks of therapy Abacavir should be discontinued immediately and patient should <u>never</u> be re-challenged.
Didanosine EC (ddI-EC)	<60 kg: 250 mg daily 60 kg: 400 mg daily	<ul style="list-style-type: none"> Renal elimination. Dose adjustment required for patients with CrCl^{***} < 60 ml/min. 	<ul style="list-style-type: none"> Nausea and vomiting Peripheral neuropathy Pancreatitis 	<ul style="list-style-type: none"> Nausea and vomiting may be transient (first 1–4 weeks). Less nausea with ddI-EC capsules. Peripheral neuropathy may be irreversible despite drug discontinuation.
Emtricitabine (FTC)	200 mg daily	<ul style="list-style-type: none"> Renal elimination. Dose adjustment required for patients with CrCl < 50 ml/min. 	<ul style="list-style-type: none"> Skin hyperpigmentation – palms of hands and soles of feet; more common in children 	<ul style="list-style-type: none"> Exclude secondary syphilis
Lamivudine (3TC)	150 mg twice daily or 300 mg daily	<ul style="list-style-type: none"> Renal elimination. Dose adjustment required for patients with CrCl < 50 ml/min. 	<ul style="list-style-type: none"> Well tolerated 	
Stavudine (d4T)	30 mg twice daily	<ul style="list-style-type: none"> Renal elimination. Dose adjustment required for patients with CrCl < 50 ml/min. 	<ul style="list-style-type: none"> Peripheral neuropathy Fat redistribution Pancreatitis Hyperlipidaemia 	<ul style="list-style-type: none"> Consider switching to another NRTI in patients with neuropathy. Peripheral neuropathy may be irreversible despite discontinuation of d4T
Tenofovir (TDF)	300 mg daily	<ul style="list-style-type: none"> Renal elimination. Dose adjustment required for patients with CrCl < 50 ml/min. 	<ul style="list-style-type: none"> Renal toxicity Decreased bone mineral density 	<ul style="list-style-type: none"> Risk of renal toxicity is greater in patients with preexisting renal insufficiency. Be sure to properly adjust dose based on CrCl. Monitor renal function (serum creatinine) closely Clinical significance of bone loss is unknown

Drug	Adult Dose	Dosage adjustment	Main adverse effects	Comments
Zidovudine (ZDV)	300 mg twice daily	Undergoes glucoronidation with subsequent renal elimination of the metabolites. Dose adjustment required for patients with CrCl < 15 mL/min	<div><div>■</div><div>■</div><div>■</div></div>	<div><div>■</div></div> Nausea, vomiting, and fatigue common in first weeks of therapy but should be transient.

* Lactic acidosis (LA) is a rare but potentially life-threatening toxicity of all NRTI/NRTIs. Risk factors include hepatic steatosis, female sex, obesity, and co-administration of d4T and ddI. Consider LA in pts with unexplained nausea, vomiting, abdominal pain, malaise, and other non-specific symptoms. Incidence varies by NRTI. If occurs, change to NRTI with lower incidence: ddI > d4T > AZT > 3TC = FTC = ABC = TDF

** CrCl=Estimated creatinine clearance

Table 2**Pivotal Efficacy Trials of Nucleos(t)ide Reverse Transcriptase Inhibitors in Treatment-Naïve Patients**

Trial^(Reference) (N)	Randomization arms	Primary efficacy end-point	Primary efficacy outcome	Comments
ACTG 384⁽⁵⁰⁾ (980)	d4T / ddI + EFV d4T / ddI + NFV AZT/3TC+EFV AZT/3TC + NFV d4T / ddI + NFV + EFV AZT/3TC + NFV + EFV	Failure of two consecutive three-drug regimens, failure of a single four-drug regimen, or premature discontinuation of the study treatment for any reason	The combination of AZT/3TC+EFV had superior virologic activity and safety profile compared to the other regimens	No benefits of the four drug regimens over AZT/3TC+EFV
GS 903⁽⁶⁰⁾ (602)	d4T/3TC+EFV TDF/3TC+EFV	VL < 400 copies/mL at week 48 using ITT analysis	84% of patients on d4T/3TC+EFV and 80% of patients on TDF/3TC+EFV had VL below 400 copies / mL at week 48	TDF combination did not meet criteria for equivalence at week 48 for the primary endpoint but equivalence was demonstrated using VL < 50 c/mL. TDF was associated with better lipid profiles, less lipodystrophy and equivalent efficacy in long-term follow up
GS 934⁽⁶¹⁾ (517)	AZT/3TC+EFV TDF/FTC+ EFV	VL < 400 c/mL at week 48 in TLOVR analysis	73% of patients on AZT/3TC+EFV and 84% on TDF/FTC+ EFV met primary efficacy end-point at week 48	TDF/FTC was virologically noninferior to AZT/3TC and had significantly less adverse events. No K65R in TDF arm
ACTG 5175⁽¹⁰³⁾ PEARLS (1571)	AZT/3TC/EFV TDF/FTC/EFV ddI/FTC/ATV	Time to treatment failure = confirmed VL > 1,000 c/mL at or after week 16	No significant difference in time to virologic failure between AZT/3TC and TDF/FTC groups	ddI/FTC+ ATV arm discontinued due to inferior efficacy
ACTG 5202⁽⁸⁴⁾ (1858)	ABC/3TC + EFV or ATV TDF/FTC + EFV or ATV	Time to virologic failure = confirmed VL > 1000 c/mL at or after 16 weeks and before 24 weeks or > 200 c/mL at or after 24 weeks.	Time to Virologic failure was significantly shorter in the ABC/3TC than TDF/FTC arm (HR=2.33, 95% CI 1.46–3.72), occurring in 57 and 26 subjects respectively	ABC/3TC arm terminated because of high virologic failure rate in patients with baseline VL > 100,000 c/mL
CNA30024⁽⁷¹⁾ (649)	ABC/3TC+ EFV AZT/3TC+EFV	VL < 400 copies/mL at week 48 in TLOVR analysis	70% of patients on ABC/3TC+ EFV and 69% of patients on AZT/3TC+EFV had VL less than 400 / mL at week 48	ABV demonstrated noninferior virologic activity and CD4 count appreciation compared to ZDV
HEAT⁽⁷²⁾ (688)	ABC/3TC+ LPV/r TDF/FTC+ LPV/r	Proportion with VL < 50 c/mL at week 48 in ITT analysis	68% of patients on ABC/3TC+ LPV/r had VL less than 50 copies/ml compared to 67% in patients on TDF/FTC+ LPV/r	TDF/FTC demonstrated non-inferior virologic activity compared to ABC/3TC

VL: (plasma HIV-1 RNA, viral load)

ITT: intent-to-treat

TLOVR: Time to loss of virologic response

ABC- abacavir, ATV- atazanavir, AZT- zidovudine, ddI- didanosine, d4T- stavudine, EFV- efavirenz, FTC- emtricitabine, NFV- nelfinavir, TDF- tenofovir, 3TC-lamivudine