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Combinations of Nucleoside/Nucleotide Analogues for HIV Therapy

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Abstract

Nucleoside and nucleotide analogues are essential for the design of effective antiretroviral regimens. There are currently many options for the selection of such drug backbones, although not all combinations will display optimal results. The concomitant administration of certain drugs should be avoided due to high rates of toxicity (ddI/d4T, ddI/TDF), antagonism (AZT/d4T, 3TC/FTC) and/or a greater risk of virological failure (ddI/TDF, ABC/TDF). The understanding of the plasmatic and intracellular metabolism of nucleoside/nucleotide analogues is crucial for deciding the optimal posology of each drug and the better dual combinations to be selected. Interferences between the pathways involved into the intracellular activation of some nucleoside/nucleotide analogues may help to understand why certain drug combinations should be avoided. **(AIDS Reviews 2004;6:234-43)**

Key words

Nucleoside analogues. Nucleotides. Purine nucleoside phosphorylase. Pharmacokinetics.

Introduction

Dual nucleoside/nucleotide analogue combinations are still the backbone of choice for most triple regimens used in the treatment of HIV infection. The many options available (there are seven nucleoside/nucleotide analogues approved for prescription) to choose the optimal combination are really welcome, and it is nowadays possible to find an effective and well-tolerated nucleoside/nucleotide backbone to design a successful triple regimen. Finally, the co-formulation of several active principles in one pill, or the development of drugs to be given once daily, have improved the efficacy of this antiretroviral drug family to a great extent.

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However, not all nucleoside/nucleotide analogue combinations are worthy to be recommended. Some associations may predispose to higher risk of virological failure, while others may lead to a higher rate of adverse effects, or present unexpected toxicities. The following review tries to go deeper into the metabolic mechanisms explaining why nucleoside/nucleotide analogues may interfere between themselves, causing adverse clinical outcomes.

Main pharmacological characteristics of nucleoside/nucleotide analogues

Zidovudine (ZDV)

This thymidine analogue has a short plasmatic (1 to 2 h)[1] and intracellular (2 to 4 h)[2] half-life. Therefore, it should be administered at least twice daily (250 or 300 mg bid). Recent reports have assessed the possible efficacy of ZDV once daily (500 or 600 mg qd) based on an intracellular half-life of 11 h for ZDV triphosphate[3]. However, other studies have shown that the virological efficacy of ZDV is compromised when given in a single dose per day[4].

As with all nucleoside analogues, ZDV requires three intracellular phosphorylations to gain antiviral activity. There is a natural accumulation of the monophosphate and diphosphate forms of ZDV into the cytoplasm, which causes a block in the natural pathway leading to thymidine triphosphate (TTP) synthesis[5]. This phenomenon explains at least in part the antiretroviral effect of ZDV – there are more chances for ZDV-triphosphate than for TTP to be incorporated into the nascent cDNA by the HIV reverse transcriptase – and the hematologic toxicity of the drug; the synthesis of cellular DNA may also be compromised. ZDV is metabolized in the liver, kidney and gut through glucuronization.

Stavudine (d4T)

The short plasma half-life of d4T, another thymidine analogue, requires twice daily administration of the drug, although there is an extended release formulation in perspective that may allow a qd posology. Most of d4T is accumulated un-phosphorylated inside the cells. While the limiting step is found at the first phosphorylation of d4T, this is not the case for ZDV as it has a higher affinity for the thymidine kinase enzyme catalyzing this reaction. For this reason, when d4T is given in combination with ZDV, the phosphorylation of the former is severely compromised and this renders the drug ineffective[6]. ZDV and d4T should never be combined. Stavudine is mainly cleared by the kidney.

Lamivudine (3TC)

This cytosine analogue is rapidly and intensely absorbed when given orally (time to C_{max} of one hour and 82% bioavailability). When 3TC is given as 150 mg bid or 300 mg qd, the C_{max} (2.1 and 3.5 µg/ml, respectively) and C_{min} (0.33 and 0.15 µg/ml, respectively) are significantly different. However, drug exposure in bid and qd posologies, as reflected by the area under the curve (AUC), is comparable (17.1 and 16.6 µg/h/ml, respectively). The intracellular C_{max} and AUC for 3TC triphosphate are similar when 3TC is given as 150 mg bid or 300 mg qd[7]. Moreover, the intracellular half-life of 3TC triphosphate is fairly long (nearly 15 h)[8]. These facts support the qd administration of 3TC. Clinical studies have proved that 3TC at doses of 300 mg qd may be used safely at least in the context of triple antiretroviral combinations[9].

Emtricitabine (FTC)

This is a recently marketed cytosine analogue, whose biochemical structure is very close to that of 3TC. However, the potency of FTC seems to be slightly higher, most likely due to its 4- to 10-fold higher affinity for the HIV retrotranscriptase[10]. Moreover, its plasma and intracellular half-lives are longer (10 and 40 h, respectively)[11]. The association of FTC with other nucleoside analogues in triple combinations has shown good antiviral efficacy.

Abacavir (ABC)

This guanosine analogue is rapidly absorbed when given orally (time to C_{max} of one hour) and it has a short plasma half-life (around one hour). It is mainly eliminated by the kidney[12]. Unlike other nucleoside analogues, ABC needs to be converted into its active metabolite, carbovir (CBV), after cytosolic deamination. The triphosphorylated form of CBV is the one showing inhibitory activity over the RT enzyme[13]. The rationale for the administration of ABC once daily (600 mg) is dependent on the long plasma and intracellular half-lives of CBV triphosphate (21 h and > 12 h, respectively)[14,15]. Recent trials have demonstrated that drug exposure and antiviral efficacy are similar, irrespective of ABC being administered qd or bid[16]. A few trials are currently ongoing using ABC qd and preliminary results have been good, although data with a longer follow up will be very valuable[17].

Didanosine (ddI)

This adenosine analogue has a major limitation in its oral bioavailability (only around 30%) and it is highly compromised in the presence of acid gastric pH[1]. This problem, however, has been satisfactorily overcome with the new enteric-coated capsule formulation, which results in similar efficacy while improving the tolerance of the older buffered tablets[18].

As with other nucleoside analogues, ddI has to be triphosphorylated to acquire its inhibitory antiviral activity. The intracellular half-life of ddI triphosphate may be as long as 40 h, which allows the drug to be given once a day[19]. No significant differences in the main pharmacokinetic parameters of ddI have been found in plasma when the drug is given as 200 mg bid or 400 mg qd[20].

The clinical efficacy of ddI once daily, along with 3TC and efavirenz (EFV), has been compared with a bid standard regimen containing AZT/3TC and EFV. The

virological results were comparable between both arms, which also validates the use of ddI plus 3TC as an optional nucleoside backbone[21].

Tenofovir (TDF)

This adenosine analogue is administered as tenofovir disoproxil fumarate, a prodrug formulation that improves the oral bioavailability and cellular penetration of the active principle. The coadministration of TDF with food increases its bioavailability by up to 40%.

Only two phosphorylations are required to get to the active form of the drug, tenofovir diphosphate. The intracellular half-life of TDF is long enough to allow its once daily administration[22].

TDF has been shown to be equally or more effective than other potent nucleoside analogues (such as d4T) in the context of protease inhibitor (PI)[23] or non-nucleoside analogue[24] regimens.

Dual nucleoside/nucleotide analogue combinations

Among the many ways to combine the seven nucleoside/nucleotide analogues described above, only a limited number of them are advisable in clinical practice. Some associations have shown higher than expected rates of virological failure or drug-related toxicities. In many cases, the mutual interference between drugs in their intracellular metabolism, and with the metabolism of the natural nucleotides, may account for these problems. A first approach to anticipate such complications with certain nucleoside/nucleotide backbones may be to avoid the use of drugs that compete with the same natural nucleotide (Table 1). This is the basis for the interference between ZDV and d4T (both thymidine analogues), 3TC and FTC (both cytidine analogues), and ddI and TDF (both adenosine analogues). Following this approach, some other potentially unwise combinations may be identified.

Recommended backbones

ZDV plus 3TC

This association is one of the most widely used nucleoside backbones, and it has been validated in multiple studies. The ACTG 384[25,26] study compared ZDV/3TC with d4T/ddI (both combinations together with EFV or nelfinavir [NFV] as the third drug) given to drug-naive subjects. This study validated EFV as an alternative to PI in first-line regimens, and indicated that ZDV/3TC performed better than d4T/ddI, as the latter was less well tolerated and equally or less effective than the former. Study 934 compared ZDV/3TC with FTC/TDF in first-line regimens also containing EFV; the 24-week results have recently been released[27]. Although the proportion of subjects with plasma HIV-RNA < 50 copies/ml was higher with FTC/TDF (73%) as compared with ZDV/3TC (65%), this was mainly due to a higher rate of ZDV-related hematological complications in the subgroup of patients with CD4 counts below 200 cells/µl, while in subjects with CD4 counts above this threshold ZDV/3TC and FTC/TDF performed similarly well.

When ZDV and 3TC are combined, the selection of resistance mutations to one drug somehow protects against the development of resistance to the other. The M184V mutation emerges rapidly, and confers high levels of resistance to 3TC; this substitution increases the susceptibility to ZDV[28] and delays the selection of thymidine-associated mutations that compromise ZDV activity[29].

Another advantage has been added to the generally good tolerance of both drugs – the co-formulation of ZDV and 3TC in one pill (Combivir) to be given twice daily.

ZDV plus ddI

As both nucleoside analogues were marketed early in the history of antiretroviral therapy, they were frequently given as dual combinations. However, in the context of HAART this association is not generally considered at first due to posology reasons (ZDV should be given twice daily with food, while ddI is given once a day and requires an empty stomach).

d4T plus 3TC

There is wide experience with this combination that is as effective as ZDV/3TC[30]. However, in recent years this association has been generally disregarded due to concerns of d4T metabolic and morphologic toxicities, and the unavailability of the d4T extended-release form for qd administration.

ABC plus 3TC

This association has recently been included as an alternative backbone in the DHHA guidelines[31]. ABC plus 3TC, given twice a day, have been used as the nucleoside backbone in the NEAT and SOLO studies, which compared NFV with fosamprenavir in drug-naive HIV-infected subjects. Besides demonstrating the su-

Table 1. Classification of nucleoside/nucleotide analogues used as antiviral agents

	Pyrimidine analogues		Purine analogues	
	Cytidine	**Thymidine**	**Adenosine**	**Guanosine**
HIV	3TC FTC ddC	ZDV d4T –	ddI TDF –	ABC – –
HBV	3TC Clevudine	Telbivudine	Adefovir	Entecavir
HCV	–	–	–	Ribavirin
CMV	Cidofovir	–	–	Gancyclovir
Herpes virus	–	Trifluridine	Vidarabine	Famcyclovir Acyclovir

periority of fosamprenavir over NFV, the ABC/3TC combination was well tolerated. The most frequent resistance mutation at failure was M184V, with other substitutions at the reverse transcriptase (such as K65R or L74V) being detected in a minority of cases (< 1%). This means that ABC/3TC failure may still leave many options for designing an effective rescue regimen with nucleoside/nucleotide analogues.

ABC/3TC has also served as the common nucleoside backbone to compare ritonavir (RTV)-boosted amprenavir (APV) with EFV as first-line regimens[32]. The proportion of subjects with plasma viremia < 50 HIV-RNA copies/ml at 48 weeks was higher with EFV (78%) than with the PI (62%), which might be due to better treatment adherence with the former. Again, the genotypic analyses at failure demonstrated that the M184V mutation was the most frequently selected change (33%), while K65R or L74V appeared very rarely.

The ZODIAC study[17] has found similar virological efficacy in drug-naive subjects starting ABC/3TC plus EFV, irrespective of the nucleoside backbone being administered once or twice daily (66 and 68% of patients, respectively, attaining < 50 HIV-RNA copies/ml at the end of follow-up).

The combination of ABC/3TC has also been compared with the classical ZDV/3TC backbone. The virological results were comparable at 48 weeks, while the recovery of CD4+ T-cells was much higher with ABC/3TC, most likely due to ZDV-related bone-marrow toxicity[33].

The recent co-formulation of ABC/3TC in one single pill (Epzicom) to be given once daily has made this combination very attractive.

ddI plus 3TC

This nucleoside backbone may be considered for once daily regimens. There are studies using ddI/3TC combined with nevirapine (NVP)[34], EFV[35] or PI[36,37], with excellent results.

A recent randomized trial has compared ddI/3TC with ZDV/3TC, given to drug-naive subjects in combination with EFV; the proportion of patients attaining undetectable viremia at 52 weeks was 74% in both groups[21].

Besides the convenience of a qd posology, the cost of ddI plus 3TC is one of the lowest among the many available combinations.

ddI plus FTC

This may be an interesting once daily nucleoside backbone, which may offer low cost, good tolerance, and potency. There is an ongoing comparative study with ddI and EFV, plus d4T or FTC[38]. Preliminary data suggest that the rate of virological failure at 48 weeks was lower in the FTC arm (5%) than in the d4T arm (13%), most likely due to a poorer tolerance of the latter (17 vs. 7%) and better adherence in patients receiving the former drug.

TDF plus 3TC

Study 903[24] compared d4T/3TC with TDF/3TC in drug-naive subjects, in both instances together with EFV. The virological results at 144 weeks tended to be slightly better for the TDF arm compared to the d4T arm (73 vs. 69% with plasma viremia < 50 copies/ml, p = NS). However, the lipid and morphological profile

was more favorable for the TDF arm. However, while in the d4T arm no nucleoside associated mutations (NAMs) were detected at failure, the K65R mutation was seen in 17% of viral rebounds on TDF, which may compromise the activity of most nucleoside analogues (except AZT) used in the rescue regimen. It is noteworthy that the selection of M184V by 3TC, which occurred in most cases of virological failure, seems to increase TDF activity[39]. Finally, regarding convenience, TDF plus 3TC may be given as two pills once a day.

TDF plus FTC

The experience with this combination is scarce, although the similarities between FTC and 3TC may predict a good efficacy and safety profile. TDF and FTC, together with Kaletra[23] or EFV[27], have been tested in drug-naive subjects with excellent results. The availability of both compounds formulated in one single pill (Truvada) has added a critical advantage to this backbone.

Suboptimal backbones

d4T plus ddI

This combination was one of the most widely prescribed backbones for many years, due to the high antiviral potency of both drugs[40]. However, the synergistic effect of both nucleoside analogues in causing mitochondrial toxicity (i.e. pancreatitis, steatohepatitis, peripheral neuropathy, lipoatrophy, hyperlactatemia) has prompted discouraging its use, especially now that many other options are available[41].

ddI plus TDF

At first sight this combination seemed to be really attractive: just two pills, high genetic barrier for resistance, good tolerance profile, and taken once a day. The first unexpected problem derived from the interaction of both drugs was a significant increase in the plasma levels of ddI (40 to 50% increase in the AUC). Therefore, it is recommended to reduce ddI doses to 200 or 250 mg daily, depending on the body weight of the patient being below or above 60 kg, respectively[42].

There were two main hypotheses to explain the pharmacokinetic interaction between ddI and TDF. One was that TDF might increase the gastrointestinal absorption of ddI[43]. Although the underlying mechanism has not been elucidated, the lack of an effect of TDF on ddI half-life and renal clearance, together with higher C_{max}, AUC and cumulative urinary excretion for ddI when given with TDF, are the arguments that support this first hypothesis.

The alternative approach to explain the interaction between ddI and TDF depends on the inhibition of ddI metabolism by TDF. This second mechanism has gained credibility and, as we will try to elucidate, may also explain other problems observed with the ddI/TDF combination. Purine nucleoside phosphorylase (PNP) is a cellular enzyme present in many tissues, especially in lymphocytes, but also in erythrocytes, granulocytes and kidney cells. PNP is responsible for the metabolism of the purines (inosine and guanine). As ddI is a purine analogue, this drug is cleared in part within the cells through PNP. On the other hand, the phosphorylated forms of TDF, which is another purine analogue, are able to inhibit PNP activity and, by doing that, TDF may increase ddI levels (Fig. 1). Not surprisingly, other antivirals that act as PNP inhibitors, such as ganciclovir, are known to increase ddI levels as well[44].

The interference of TDF in the metabolism of ddI may also explain the higher incidence of ddI-related toxicities reported in subjects exposed to this combination. Reports of higher than expected rates of pancreatitis[45], lipoatrophy[46] and hyperglycemia[47], have attracted much attention in recent months, even when using weight-adjusted doses of ddI. In vitro studies have shown a direct relationship between ddI levels and the intracellular concentration of dideoxyadenosine-triphosphate (ddATP)[48], the active form of ddI and also a potent inhibitor of the γ-DNA polymerase. Hypothetically, the reduction in the cellular catabolism of ddI through PNP inhibition by TDF could enhance ddI-related toxicities by facilitating the ddATP inhibition of mitochondrial DNA synthesis (Fig. 1).

More intriguing are several recent reports which have found that, despite optimal virological suppression with regimens containing ddI/TDF, a significant proportion of patients show a paradoxical decline in their CD4 counts[49,50]. Again, the interference of TDF in the metabolic pathways of the purines may be responsible for this unexpected observation. As shown in figure 1, the TDF-MP and TDF-DP inhibition of PNP-mediated catabolism of IMP and GMP will prime the final production of GTP. This molecule has a high affinity for ribonucleotide reductase (RNR), the enzyme responsible for deoxyribonucleotide synthesis. These molecules are essential for DNA synthesis and cell mitosis.

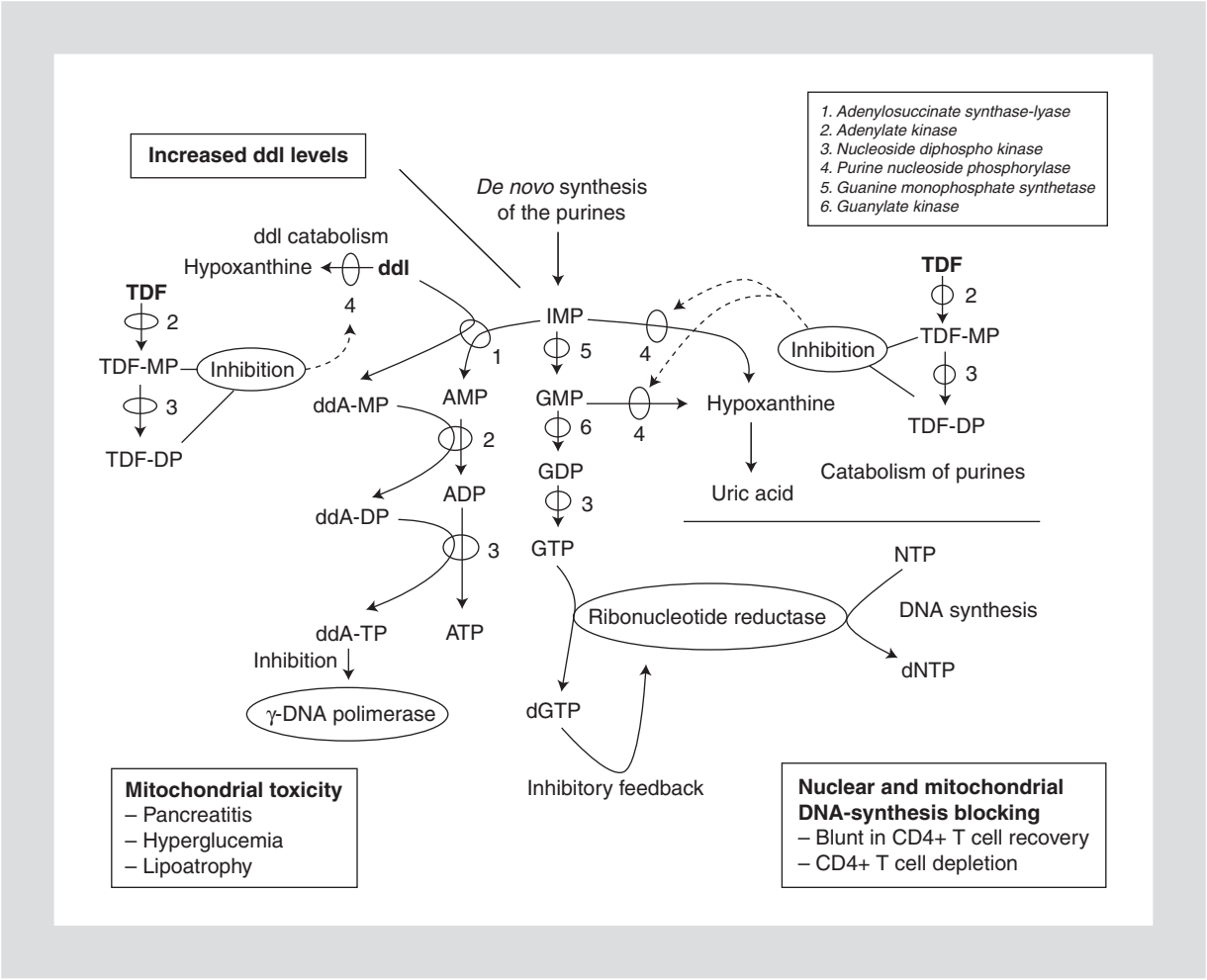

Figure 1. *Hypothetical mechanism for toxicities, including CD4+ T cell depletion, when combining ddI and TDF.*

GTP plays a pivotal role in nucleotide vs. deoxynucleotide intracellular equilibrium, because dGTP exerts a potent inhibitory feedback over the RNR. As a result, the increase in dGTP levels, as the last consequence of PNP inhibition, might cause lower RNR activity and, by doing that, the capability of T lymphocytes to proliferate could be largely impaired. The final result should be a reduction in the capability of CD4+ T-cells to proliferate. Furthermore, in a PNP knockout mice model, it has been demonstrated that the accumulation of dGTP may also predispose to CD4+ T-cell depletion by inflicting mitochondrial DNA damage[51]. According to these findings, the accumulation of dGTP would preferentially occur at mitochondrial level, where dGTP would cause mitochondrial RNR inhibition. The diminution in the ability to repair mitochondrial DNA caused by RNR malfunction would finally precipitate cellular apoptosis and CD4+ T-cell depletion.

Supporting these explanations, it is worth reminding that there is a congenital immunodeficiency syndrome caused by the absence of PNP. Among other signs and symptoms, children carrying this genetic defect usually die in their early infancy due to severe and selective CD4+ T-cell depletion[52].

Finally, regimens containing ddI/TDF have shown high rates of virological failure, either in triple nucleoside/nucleotide combinations or in association with other antiretroviral agents. In a small open label study, 24 drug-naive subjects started ddI/TDF/3TC. The follow-up was interrupted prematurely after 12 weeks due to an incidence of virological failures as high as 91%. Moreover, at viral rebound all patients carried the M184V mutation, and half of them K65R[53]. In another study, two once daily backbones (ddI/TDF vs. ddI/3TC), given together with EFV, were compared in drug-naive subjects with CD4 counts below 200 cells/μl and viral

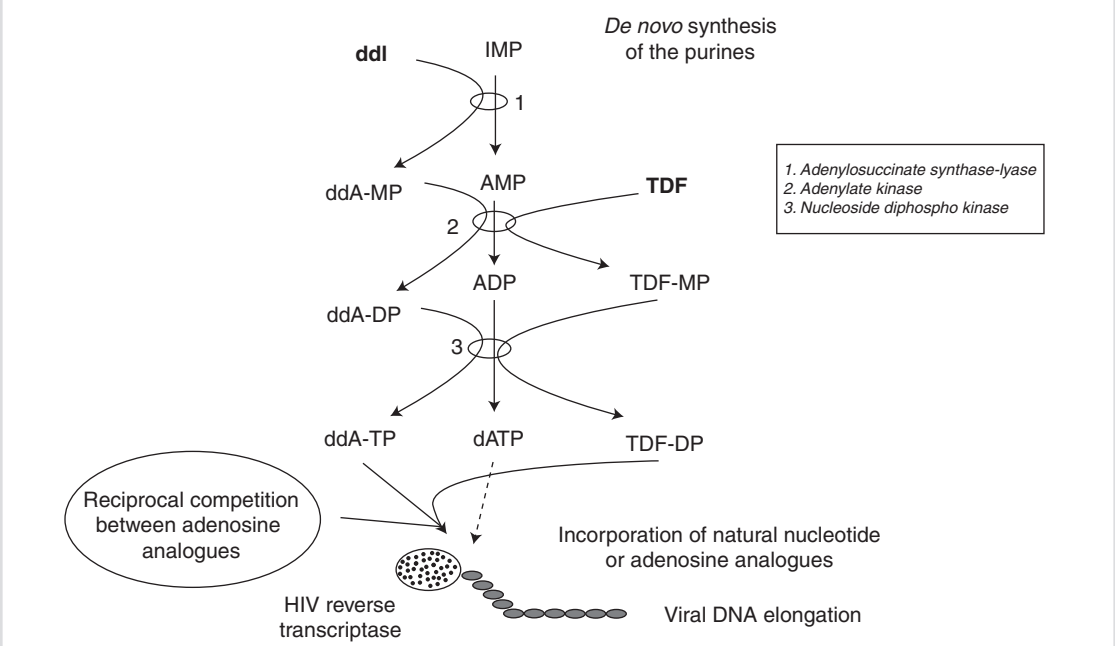

Figure 2. *Metabolic pathways for ddI and TDF, and possible mechanism for a higher risk of virological failure.*

loads above 5-log HIV-RNA copies/ml at baseline[54]. Again, the study was interrupted at 12 weeks due to a 13% rate of virological failure in the ddI/TDF arm, whereas all subjects in the ddI/3TC arm had attained undetectable viremia. As good treatment adherence was ensured with MEMSCAP assessment, and all failing-patients on ddI/TDF harbored resistance mutations, a possible interference between ddI and TDF was postulated as the main mechanism underlying this high rate of virological failure.

As adenosine analogues, both ddI and TDF share the metabolic pathway of ATP synthesis, and therefore the enzymes responsible for the corresponding phosphorylation steps (Fig. 2). As ATP is essential for many cellular reactions, its production is highly regulated. The interference between ddI and TDF in the two final phosphorylation reactions would cause at least one of the drugs to be in relative disadvantage with respect to ATP. The final result will be a better access to the reverse transcriptase by the natural nucleotide (dATP) than for the nucleoside (ddI) or nucleotide (TDF) inhibitors, which may be somewhat similar to using just one instead of two drugs. Figure 3 summarizes the main caveats related with the combination of ddI and TDF.

ddI plus ABC

There is no experience with this combination as a nucleoside backbone in the context of NNA- or PI-containing HAART. The fact that both drugs may select for the same resistance mutations (K65R or L74V) makes this combination inadvisable for routine clinical practice.

TDF plus ABC

This combination may be attractive, as it can be given once a day and no significant problems of tolerance may be expected. When associated with NNAs or PIs, TDF/ABC seems to offer good virological efficacy, which does not occur if TDF/ABC is given together with another nucleoside analogue. This affirmation is derived from the results of the RECOVER study[55], in which a total of 101 patients having undetectable viremia moved to ABC/TDF due to bad tolerance of the prior triple regimen. Overall, 50 patients received ABC/TDF plus a NNA or a PI, and only three showed virologic failure at 24 weeks. Conversely, eight out of 51 patients (16%) on ABC/TDF plus a

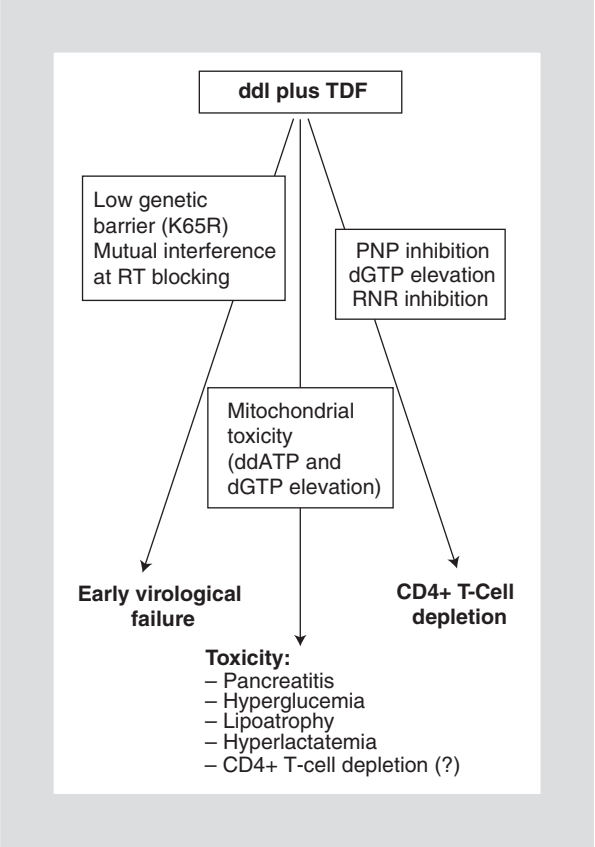

Figure 3. *Main limitations of the association of ddI with TDF. PNP, purine nucleoside phosphorylase; RNR, ribonucleotide reductase.*

third nucleoside analogue experienced virological failure.

The ESS30009 trial[56] compared TDF/ABC given with 3TC or EFV, and was prematurely stopped due to unacceptably poorer results with the former combination. The proportion of subjects with virologic failure (< 2 log copies/ml decline in viral load or viral rebound after undetectable viremia) at eight weeks was 49% with TDF/ABC/3TC and 5% with TDF/ABC/EFV ($p < 0.001$). Moreover, all subjects failing in the 3TC arm presented resistance mutations (M184V in 100% and K65R in 64%). The Tonus study[57] found similar results, as 12 of 36 naive subjects (33%) did not attain undetectable viremia after 24 weeks on TDF/ABC/3TC. The determination of drug levels in plasma ensured good treatment adherence, despite all failures carrying the K65R and M184V mutations.

High rates of viral rebound have also been reported when TDF/ABC/3TC is given as a simplified regimen to subjects already with undetectable viremia. In a retrospective study[58], all eight subjects moving to this triple nucleos(t)ide combination from an effective regimen showed early virological failures, with the selection of K65R and M184V mutations. In view of these data, and besides the hypotheses of a low genetic barrier (K65R compromises both TDF and ABC), an underlying phenomenon of intracellular drug interference could help to explain these high rates of virologic failure with TDF/ABC.

Triple nucleoside/nucleotide regimens may be considered weaker than other combinations that include drugs of distinct families, as targeting different viral enzymes and/or in different sites will reduce the chances of inhibitory competition between drugs. In the particular case of TDF/ABC/3TC, viral escape may occur with the selection of just two nucleotide substitutions, the one leading to M184V and another to K65R, that confer resistance to the whole triple regimen.

The plasma pharmacokinetics of ABC and TDF do not seem to be affected if both drugs are administered together[59]. However, at the intracellular level it is of concern that the antiviral activity of CBV triphosphate (the active form of ABC) might be compromised by TDF (Fig. 4). As previously mentioned, the phosphorylated forms of TDF inhibit the activity of the PNP[44], which is the enzyme responsible for the degradation of purines into uric acid. The inhibition of PNP by TDF-MP and TDF-DP will cause the priming of the metabolic pathway leading to GTP and dGTP formation. This last molecule is the natural competitor of CBV-TP for the viral RT enzyme. Therefore, even without a reduction in the intracellular level of CBV-TP, impairment in its antiviral activity might occur[60]. The access of the natural nucleotide (dGTP) to the RT might be facilitated by the inhibition of the PNP by TDF. Although this interference might not suffice to cause virological failure, this may occur when TDF and ABC are associated to a drug, such as 3TC, with a low genetic barrier and relatively weak antiviral activity. If the choice is a drug with a higher genetic barrier or a different mechanism of action (such as a NNA or PI) the deleterious intracellular interaction between TDF and ABC is masked and not clinically relevant.

Conclusions

Nucleoside/nucleotide analogues are currently essential components for designing antiretroviral regimens. The availability of a wide variety of these drugs allows optimizing their efficacy and tolerance. Not every possible combination of these drugs is worthy of use, the mutual interference at intracellular level being

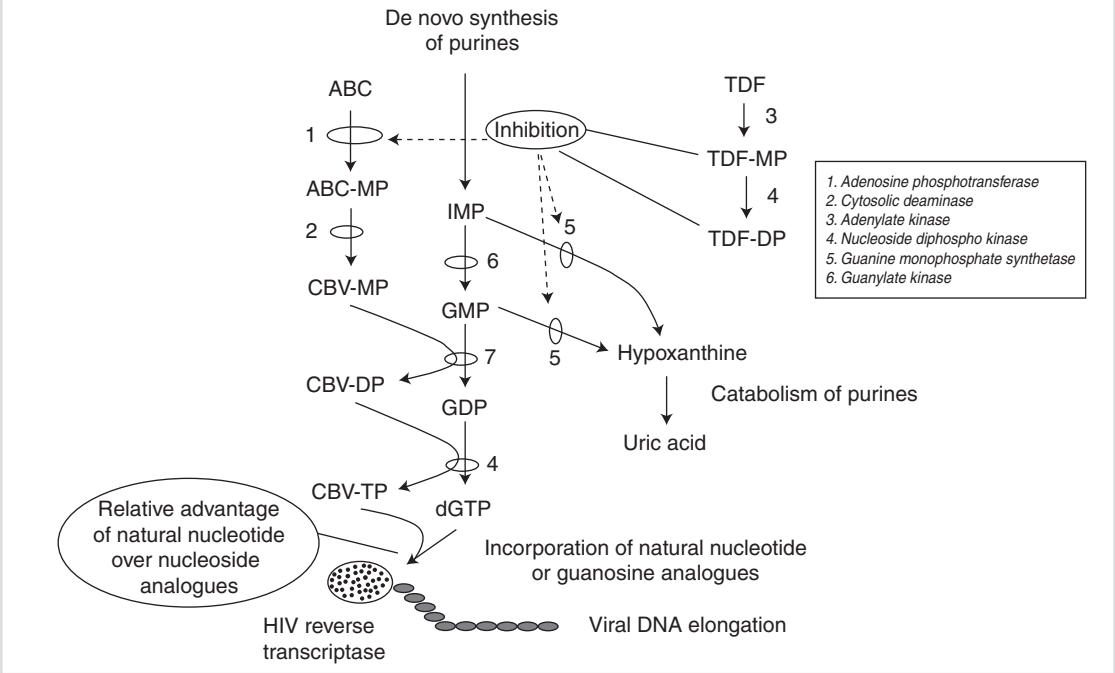

Figure 4. *Metabolic pathways for ABC and TDF, and possible mechanisms involved in its higher risk of virological failure.*

the most frequent cause of incompatibility. The difficulties of measuring cytoplasmic drug levels make nucleoside/nucleotide analogue interactions a challenging field for intensive investigation.

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