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Didanosine Enteric-Coated Capsule

Current Role in Patients with HIV-1 Infection

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Abstract

Didanosine, which is a synthetic nucleoside analogue intracellularly phosphorylated to the active metabolite, inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate. Currently, didanosine is mainly provided as an enteric-coated capsule. *In vitro*, the molecule is active against laboratory strains and clinical isolates of HIV-1 in resting and activated T cells and monocyte/macrophages. Didanosine may select for resistance mutations that may render the drug inactive against the virus; L74V and K65R remain as the main didanosine-related mutations. *In vitro*, phenotypic susceptibility to didanosine was decreased beyond a defined fold change clinical cut-off (1.7), and it is considered that genotypic resistance exists when five thymidine-associated mutations or four plus M184V are present. *In vivo*, clinical studies have shown that didanosine retains significant antiviral activity in patients who have up to five nucleoside analogue mutations at baseline. Didanosine is useful in patients with no previous therapy, as well as in experienced patients in whom one or more antiretroviral regimens has failed.

Enteric-coated didanosine is taken once daily, its co-administration with food has been recently evaluated and a reduction of the efficacy of the antiretroviral treatment was not observed. Administered with lamivudine (or emtricitabine), it can be considered a good alternative for use in the nucleoside analogue backbone included in combination therapies for antiretroviral-naive patients. Didanosine could be used in initial treatments for patients intolerant of zidovudine, abacavir or tenofovir. It can be included in once-daily combination regimens, which are more convenient and patient friendly.

Prospective, observational and open-label studies, as well as clinical trials (with durations between 24 and 96 weeks), have demonstrated the safety and efficacy of didanosine plus lamivudine (or emtricitabine) plus efavirenz (or nevirapine) in previously untreated HIV-1-infected patients. The administration of didanosine to treatment-experienced patients has been evaluated in two different contexts: patients in whom previous therapies have failed (rescue therapy) and those with controlled viraemia who are switched to a didanosine-containing regimen for simplification.

Adverse events associated with the administration of didanosine have been well known since the initial clinical trials with the drug. Gastrointestinal intolerance, peripheral neuropathy and hyperamylasaemia/pancreatitis were the most frequently reported. In the highly active antiretroviral therapy (HAART) era, the rate of adverse events has decreased. The tolerability of didanosine has been clearly improved with the development of the enteric-coated capsule. Severe manifestations of mitochondrial toxicity, including lactic acidosis and abnormal fat distribution, are rare complications, and occur most frequently when didanosine is used in combination with stavudine.

Didanosine was the second drug used in the treatment of HIV-1 infection. Its demonstrated activity in patients who had never been treated, as well as in those who had previously received and then stopped responding to zidovudine, led to the widespread use of didanosine early in the era of antiretroviral therapy. At that time, concerns were raised regarding two aspects of the drug. First, it was poorly tolerated, with frequent gastrointestinal disturbances that caused discontinuation in many instances. The interaction between didanosine and food meant that the drug had to be taken in fasting conditions, thus increasing the poor tolerance. These effects were related to the formulation of the drug and the buffer used. Secondly, neuropathy and pancreatitis, occasionally fatal, were identified as significant adverse events associated with didanosine. Risk factors for the development of these severe adverse events that can help to avoid their development have since been identified.

Currently, the situation for didanosine has changed completely. The introduction of didanosine as enteric-coated capsules (didanosine-EC) has led to the virtual elimination of digestive intolerance. The absence of the buffer in the new formulation is responsible for this advantage. In addition, some clinical studies have shown that the administration of didanosine-EC with food is not associated with a decrease in the virological efficacy of the drug. Recent randomised clinical trials have shown the efficacy and the lack of significant toxicity of triple combination regimens that include didanosine-EC in different clinical contexts (treatment-naive and -experienced patients).

This article reviews didanosine-EC, emphasising the most recently generated clinical data on efficacy and safety.

1. Drug Profile

Didanosine is a synthetic purine nucleoside analogue that inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate, and by causing DNA chain termination once incorporated into the viral DNA.

Currently, the most widely used formulation is VIDEX®EC[1], enteric-coated beadlets that result in a delayed release of the drug, available in four different strengths: 125, 200, 250 and 400mg, administered once daily.[1] Dispersible tablets are still available in several countries.

Didanosine is an inosine derivative, 2′,3′-dideoxyinosine, analogue to the natural nucleoside deoxiadenosine, but lacking the 3′-hydroxyl group (-OH), as shown by its structural formula (figure 1). The most relevant chemical characteristics of didanosine are summarised in table I.[1]

The absence of stability of didanosine at acidic pH, due to the lability of the *N*-glycosidic bond, was a problem with previous formulations of the drug that required co-formulation with buffers. An added inconvenience was that the substances used for buffering the tablets and avoiding the degradation of didanosine in the stomach acidic milieu were responsible for some of the unwanted gastrointestinal adverse effects of the drug. Nowadays, this fact is circumvented with the use of the enteric-coated formulation.

1.1 Pharmacodynamic Characteristics

1.1.1 Mechanism of Action

Didanosine enters the target cell by means of a nucleoside transporter protein,[2] as do natural nucleosides. Once in the cytoplasm, it is converted to the active compound, dideoxyadenosine-5′-triphosphate (ddATP), through a multistep process carried out by cellular enzymes, of which the virus takes advantage. First, didanosine is monophosphorylated

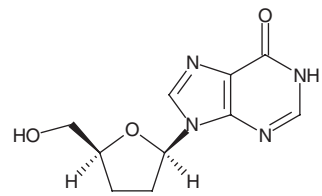

Fig. 1. Structural formula of didanosine (2′, 3′-dideoxyinosine).

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Chemical characteristics of didanosine

Appearance	White crystalline powder
Molecular formula	$C_{10}H_{12}N_4O_3$
Molecular mass	236.2
Aqueous solubility (25°C; pH = 6)	27.3 mg/mL
Stability in acidic solutions	No

to ddIMP, then aminated to ddAMP and after two more phosphorylations, ddATP is produced. This tri-phosphate form inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate (dATP) because of higher affinity for the enzyme,[3] and by causing DNA chain termination once incorporated into the viral DNA, as the lack of the 3′-hydroxyl group (-OH) precludes further addition of nucleotides.

1.1.2 In Vitro Antiviral Activity

This topic has been previously reviewed and updated in detail.[4-6] Briefly, didanosine is active against laboratory strains and clinical isolates of HIV-1 in resting and activated T cells and monocyte/macrophages. The concentration that produced 50% inhibition (IC_{50}) ranged from 2.5 to 10 μmol/L in lymphoblastic cell lines and 0.01 to 0.1 μmol/L in monocyte/macrophage cell cultures.

1.2 Pharmacokinetic Characteristics

As pharmacokinetic data of didanosine have been reviewed and updated previously,[4-6] this review focuses on the more recent contributions with special emphasis on the enteric-coated formulation. As the main pharmacokinetic parameters that could be affected by the new enteric-coated formulation are those related to liberation and absorption, and the corresponding bioequivalence, these studies are discussed.

1.2.1 Liberation

The liberation of didanosine is determined by its current gastric-resistant presentation. Didanosine enteric-coated capsules contain enteric-coated beadlets,[1] formulated to protect didanosine from the stomach acid pH to which its *N*-glycosidic bond, thus the didanosine molecule, is labile. The capsule is dissolved in the stomach but the enteric coating of didanosine beadlets results in the liberation of didanosine in the duodenum where the pH increases and didanosine is stable and soluble; this is also the main site of absorption of the drug, although absorption continues throughout the small intestine.

1.2.2 Absorption: Effect of Food

Didanosine generally has a linear dose-related pharmacokinetic profile over the normal dose range in HIV-1-infected patients, as previously reviewed, and there is no accumulation in plasma or urine.[5,6]

Following the administration of a buffered formulation, didanosine is rapidly absorbed and peak plasma concentration (C_{max}) is achieved after 0.5–1.5 hours.[1] C_{max} ranged from 0.52 to 2.79 mg/L after multiple oral doses (125–375mg twice daily) in HIV-1-infected adults.[6] Of note, there is considerable interindividual variability in the absolute bioavailability of didanosine in HIV-1-infected patients, ranging from 21% to 54%, because of differences in gastric motility and transit time for the buffered formulations.[6]

The bioequivalence of didanosine-EC capsules versus buffered tablets was assessed in healthy volunteers and HIV-1-infected patients in two separate randomised, open-label, two-way crossover studies.[7] Data from these studies demonstrated that both formulations were bioequivalent with respect to exposure to the drug, measured as area under the plasma concentration-time curve (AUC) values, showing that the enteric-coating and antacids offered similar protection. There was no bioequivalence in terms of C_{max}, which was lowered by approximately 40% for the enteric-coated capsules. Also, the rate of absorption was lower and it took longer to reach C_{max} (time to maximum concentration [t_{max}] increased from approximately 0.67 to 2.0 hours), but plasma concentrations beyond this timepoint were higher in both healthy and HIV-1-infected individuals (1.4- to 2.6-fold), compared with the buffered tablets. Pharmacokinetic parameters for didanosine-EC for healthy volunteers and HIV-1-infected patients are summarised in table II.[7]

The administration of didanosine with meals reduces its absorption by up to 50% as a result of degradation of the drug, stimulated by the acid secretions and the delay on the gastric flow induced by

Table II. Mean ± SD pharmacokinetic parameters of didanosine enteric coated capsules in healthy volunteers (n = 46) and HIV-1-infected patients (n = 30)[7]

Parameter	Healthy volunteers	HIV-1-infected patients
C_{max} (ng/mL)	1427 ± 774	933 ± 434
t_{max} (h)[a]	2.33 (1.00–6.00)	2.00 (1.00–5.00)
AUC (h • ng/mL)	3587 ± 1296	2432 ± 919
$t_{½}$ (h)	1.70 ± 0.58	1.60 ± 0.41

a Median (range).

AUC = area under the concentration-time curve; **C_{max}** = peak plasma concentration; **$t_{½}$** = half-life; **t_{max}** = time to maximum concentration.

food. This effect is of much less concern with enteric-coated capsules taken with food, as C_{max} and AUC were reduced by approximately 46% and 19%, respectively.[1] A study carried out to evaluate the effect in the bioavailability of didanosine-EC of meals with different fat content (taken at different times before and after the drug) concluded that the bioavailability was reduced by approximately 20–25% with food.[8] Currently, the recommendation is to take didanosine-EC in the fasting state,[1] which is a major drawback.

There are few studies evaluating the effect of food and the consequent decrease in bioavailability on the antiviral activity of didanosine, especially with the once-daily enteric-coated capsules. Although a reduction in the plasma concentration of didanosine could be translated into a reduction in the intracellular concentration of the active metabolite,[9] the extended intracellular half-life of the drug[10] could circumvent it and not affect its antiviral activity. Moreover, this food effect could be diluted when administering didanosine-EC in triple combination regimens. In this respect, there are at least two pilot studies where the use of didanosine-EC dosages below the usual (300mg instead of 400mg once daily) were not associated with a loss of efficacy.[11,12] Moreover, two recently communicated cohort studies, one retrospective[13] and the other one prospective,[14] showed no association between the administration of didanosine-EC with food and a reduction of the efficacy of the antiretroviral treatment. A pilot, open-label, randomised study of didanosine-EC capsules administered with a fatty meal (group 1, n = 10) or on an empty stomach (group 2, n = 11) in treatment-naive chronically HIV-1 infected individuals has been recently reported.[15] To assess the efficacy, the initial rate of decline in plasma viral load was followed and plasma concentrations of the drug were measured. The initial rates of decline in the two groups were identical (0.2 $\log_{10}$ at day 3; 0.7 $\log_{10}$ at day 7). In this pilot study, the administration of food did not have any effect on the plasma drug concentrations or the antiviral activity of enteric-coated didanosine.[15] Moreover, preliminary results from a randomised, open-label clinical trial have shown that, at week 24, didanosine-EC plus lamivudine plus efavirenz administered once daily with food provided similar antiviral efficacy to zidovudine plus lamivudine (as Combivir®) plus efavirenz.[16] It should be noted that plasma concentrations of other nucleoside reverse transcriptase inhibitors (NRTIs) are also significantly reduced when administered with food to the same extent as didanosine-EC, including zidovudine (20%) or zalcitabine (up to 27%); no fasting administration has been recommended, nor is there evidence of a reduction in efficacy.[17-19]

Given these facts, we consider that didanosine-EC can be given with food in order to avoid food restrictions that would complicate the choice of accompanying drugs. This would also take advantage of the good resistance profile and potential improvement in adherence when included in a once-daily regimen without compromising its antiviral activity.

1.2.3 Distribution

These issues have been previously reviewed.[5] Binding of didanosine to plasma proteins is minimal (5%), allowing adequate tissue distribution. The volume of distribution at steady state is 54L in HIV-1-infected adults. It only minimally crosses the placental and blood-brain barriers, achieving 20% and 50% of the maternal circulating levels in the placental and fetal circulation, respectively, and 21% in cerebral spinal fluid compared with plasma.

1.2.4 Metabolism

The metabolism of didanosine in HIV-1-infected patients has not been fully determined. Previously available data from *in vitro* and animal studies sug-

gested that didanosine metabolism followed the same pathways responsible for the clearance of endogenous purines,[1,5] or it was partially metabolised to ddATP or uric acid.[5]

Recently, some light has been shed on this issue. In a study carried out to elucidate the mechanism of interactions between didanosine and allopurinol, ganciclovir or tenofovir,[20] the authors compiled evidence regarding didanosine metabolism by means of purine nucleoside phosphorylase (PNP), the enzyme involved in the purine nucleoside salvage pathway. The main observations are that didanosine is a substrate for PNP in enzymatic assays, it is rapidly degraded, forming products consistent with PNP phosphorolysis, and that radiolabelled hypoxanthine appears in dogs after treatment with ^{14}C-labeled didanosine. Moreover, the erythrocyte has been suggested by the authors as the main site of metabolism because of its high PNP content. Figure 2 shows this metabolic pathway of didanosine.[20]

1.2.5 Elimination

Didanosine has a short plasma half-life, ranging from 0.5 to 2.74 hours. As expected, in the enteric-coated capsules bioequivalence study, the half-life was not modified by the formulation of didanosine, being 1.7 and 1.6 hours for healthy volunteers and HIV-1-infected patients, respectively.[7]

Didanosine has a mean urine excreted unchanged fraction of 18%,[1] but up to 30–50% of a given dose is excreted unchanged by glomerular filtration and tubular secretion.[21] Total body clearance in adults after a single 300mg oral dose of the buffered formulation was 20.1–22 L/h.[5]

Data obtained using didanosine buffered tablets indicate that the apparent oral clearance decreases and the terminal elimination half-life increases as creatinine clearance decreases, so the didanosine dose should be adjusted according to the renal impairment.[1]

A peculiar property of didanosine triphosphate active compound is its long intracellular half-life (>25 hours) when compared with other NRTIs.[10] This characteristic allows its use once daily, despite its short plasma half-life.

1.3 Clinically Relevant Drug Interactions

As previously reviewed, buffered didanosine formulations showed significant interactions with

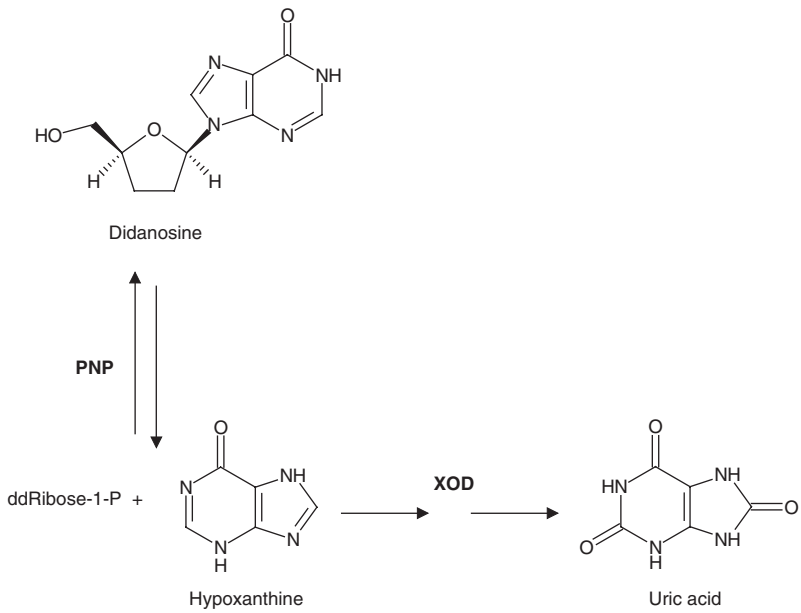

Fig. 2. Metabolic pathway of didanosine. **PNP =** purine nucleoside phosphorylase; **XOD =** xantine oxidase.

itraconazole, ketoconazole, ciprofloxacin and indinavir.[6] Most of these reported interactions were due to the added buffers of the older formulations and the consequent pH increase or the quelation exerted by the buffer accompanying di/trivalent cations. Moreover, new antiretroviral drugs have been developed and new didanosine interactions have been studied. In this context, we present an update on the relevant interactions between didanosine-EC and concomitantly administered drugs.

1.3.1 Indinavir, Ketoconazole and Ciprofloxacin

Indinavir, ketoconazole and ciprofloxacin were selected as representative drugs that interact with antacids, either by decreased solubility at a more alkaline stomach pH (indinavir, ketoconazole) or by quelation (ciprofloxacin), to study the effect of concomitant didanosine administration.[22] Healthy volunteers were enrolled in three separate open-label, single-dose, two-way crossover studies and randomised to indinavir (800mg), ketoconazole (200mg) or ciprofloxacin (750mg), or the same doses plus didanosine-EC 400mg. No absorption interactions were observed in any of the three studies. The authors concluded that didanosine-EC can be administered safely with drugs that interact with antacids. Absence of interaction with indinavir/ritonavir was further confirmed by a recent study.[23]

1.3.2 Methadone

Previous formulations of didanosine, when administered with methadone, experienced a significant reduction in levels of didanosine, requiring an increase in buffered didanosine dose, but this interaction is no longer observed with the didanosine-EC capsules.[24,25]

As previously mentionted in section 1.2.4, didanosine is metabolised by PNP and the inhibition of PNP by ganciclovir, allopurinol and tenofovir has been established as the mechanism underlying didanosine interaction with these drugs.[20]

1.3.3 Ganciclovir

When buffered didanosine and ganciclovir are administered together,[24] the AUC of didanosine is increased by 50–111%. Also, if didanosine is administered 2 hours prior to oral ganciclovir, the AUC of the latter is diminished by 21%. Unfortunately, no appropriate dose administration for this combination has yet been established. To our knowledge, there are no available data regarding didanosine-EC. As valganciclovir is quickly transformed to ganciclovir we can assume that the previous statements also apply. Caution is advised when administering didanosine, even as the EC formulation, and valganciclovir/ganciclovir concomitantly in case didanosine toxicity appears.

1.3.4 Allopurinol

Co-administration of allopurinol and didanosine increases the AUC of didanosine beyond 100% by inhibition of didanosine metabolism,[20] so a reduction of didanosine dose by 50% is recommended in order to lower the risk of toxicity, mainly pancreatitis and neuropathy.

1.3.5 Tenofovir

When administered together, no effects are observed in tenofovir pharmacokinetics but didanosine concentrations are increased by 44–60%,[1,26] regardless of the didanosine formulation used, as a result of the inhibition of PNP-mediated metabolism.[20,26] A dose reduction of the enteric-coated formulation is therefore recommended when the two drugs are administered together, as follows: adults weighing ≥60kg with creatinine clearance ≥60 mL/min: 250mg; adults weighing <60kg with creatinine clearance ≥60 mL/min: 200mg taken once daily together with tenofovir and a light meal or fasted. In addition, monitoring for didanosine toxicity is recommended. Of note, the combination of didanosine and tenofovir has been associated with CD4+ cell declines or blunted CD4+ cell responses, as recently reported,[27-29] although other authors have documented the absence of poor immunological response in this setting when didanosine was combined using the 250mg dose.[30] In the event of such immunological failure, the removal of one of the drugs is recommended.[24]

1.3.6 Ribavirin

Co-administration of didanosine and ribavirin is not recommended, as ribavirin increases the intracellular concentrations of the active metabolite of

didanosine, causing severe toxicities such as pancreatitis and lactic acidosis, and increasing the risk of neuropathy.[24,31-34] As a general rule, caution and close monitoring is recommended when didanosine is administered with other pancreatitis-inducing drugs, mainly in the context of HIV-1 infection.[24]

1.3.7 Atazanavir or Atazanavir/Ritonavir

Although no significant interaction exists between the two drugs, it is recommended that atazanavir be taken with food. The administration of didanosine-EC in this context (atazanavir and food) decreases the AUC of didanosine-EC by 34%, while no changes are observed in atazanavir concentrations. The recommendation is to take both drugs separately, atazanavir with food and didanosine-EC in fasting conditions.[24]

1.3.8 Tipranavir/Ritonavir

Administration of tipranavir/ritonavir and didanosine-EC produced a 10% decrease in didanosine concentrations and a 34% reduction of trough tipranavir concentrations. Although this study was carried out with doses of boosted tipranavir other than the US FDA-approved dose of 500/200mg, it is recommended that these drugs should be taken at least 2 hours apart from each other.[24]

1.4 Resistance

Didanosine may select for resistance mutations that could render the drug inactive against the virus. The mutations selected by the drug may affect its activity by different mechanisms (table III). The International AIDS Society-USA (IAS-USA) Drug Resistance Mutations Group periodically updates the HIV-1 drug resistance mutations list. In the latest version, L74V and K65R remain as the only didanosine-related mutations, although other mutations are clearly related with the drug.[35]

1.4.1 L74V

L74V is the main mutation associated with didanosine resistance, but it only confers low-to-intermediate phenotypic resistance (fold change: 2–5). Although it has been associated with *in vivo* virological failure in patients treated with didanosine monotherapy,[36] its detection remains quite infrequent and was mainly selected before the highly active antiretroviral therapy (HAART) era when didanosine was used alone.[37-39] More recently, the Jaguar trial, in which 168 patients were randomly assigned to receive didanosine (n = 111) or placebo (n = 57) added to their currently failing regimen for 4 weeks, has shown that despite its low frequency, the presence of L74V precluded a significant reduction in HIV-1 plasma RNA.[40,41]

1.4.2 K65R

The presence of K65R is associated with *in vitro* decreased susceptibility to the drug.[39] *In vivo*, as assessed by the Jaguar study, despite the low frequency of K65R, the addition of didanosine was not associated with significant virological response.[40,41]

1.4.3 Thymidine-Associated Mutations

Multi-NRTI resistance mutations, also known as nucleoside analogue-associated mutations (NAMs), are associated with resistance to multiple NRTIs.[35] Among them, thymidine-associated mutations (TAMs) are the subset selected by the thymidine analogues zidovudine and stavudine, comprising M41L, D67N, K70R, L210W, T215Y/F and K219Q/E. TAMs are associated with cross-resistance to all currently approved NRTIs.[35,42] The level and the extent of resistance produced by the presence of TAMs depend on the pattern of accumulation of TAMs (D67N/K70R/K219Q/T215F vs M41L/L210W/T215Y), the number of accumulated TAMs and the accompanying mutations.[42] *In vitro* phenotypic susceptibility to didanosine was de-

Table III. Didanosine-associated resistance mutations

Mutations that allow the elongation of the chain (decreased affinity of the drug)	L74V, K65R
Mutations that increase the excision (pyrophosphorolysis)	M41L, D67N, K70R, L210W, T215Y/F and K219Q/E
Multiresistance mutations	T69SSS, Q151M complex
Other mutations	E44D, V118I

creased beyond a defined fold change clinical cut-off (1.7) when five TAMs or four TAMs plus M184V were present in a large collection of clinical isolates.[43] *In vivo*, the Jaguar study showed that didanosine retained significant antiviral activity in patients who had up to five NAMs at baseline and that the presence of three of the following TAMs (M41L, D67N, L210W, T215Y/F and K219Q/E) was associated with resistance to didanosine.[35,40,41] Similarly, a smaller study in which didanosine was administered as intensification in 40 patients with virological failure, showed that didanosine retained substantial activity when the number of NAMs or TAMs was below four.[44] The genotype score derived from the Jaguar study showed that the presence of K70R and M184V mutations was not associated with a decreased virological response to didanosine; moreover, these mutations were associated with a better response.[41] The results from an observational HIV-1-infected cohort of patients (with phenotypic resistance testing after a virological failure leading to a switch to didanosine-containing HAART) highlight that while the presence of M184V did increase the fold resistance of HIV-1 to didanosine, these changes appeared to be lower than the clinically relevant threshold for phenotypic resistance for this drug.[45]

1.4.4 Other Mutations

An *in vitro* phenotypic study carried out in a panel of site-directed mutagenesis constructs applying a biological susceptibility fold change cut-off of 3.5 for didanosine showed that the presence of three TAMS plus E44D and V118I was associated with resistance.[46] The 69 insertion complex confers resistance to all NRTIs when present with one or more TAMs at codons 41, 210 or 215. Again, the Jaguar study showed that in the small subset of patients with the triple insertion at position 69, this change was associated with a reduced response to didanosine.[40,41] Another group of mutations associated to multi-resistance to all NRTIs except tenofovir is the Q151M complex, which includes A62V, V75I, F77L, F116Y and Q151M.[35]

2. Clinical Uses

Didanosine has been shown to be useful in patients with no previous therapy, as well as in experienced patients in whom one or more antiretroviral regimens have failed. The first clinical trials with didanosine monotherapy or dual nucleoside combination included both groups of patients. The overall conclusion of these early studies was that initiation of therapy with didanosine was associated with a better response rate than initiation with zidovudine, and that didanosine was useful in the treatment of patients in whom previous zidovudine therapy had failed. Dual combination of zidovudine plus didanosine and stavudine plus didanosine were shown to be superior to zidovudine plus zalcitabine or zidovudine plus lamivudine, respectively, in adequately designed clinical trials.

Monotherapy or dual nucleoside combinations that included didanosine were soon changed to triple combinations. Multiple clinical trials have evaluated the use of didanosine-EC in triple drug regimens in treatment-naive and -experienced HIV-1-infected patients. We review the available data for the two groups of patients in order to define which are the optimal candidates to be combined with didanosine-EC.

2.1 Studies in Treatment-Naive HIV-1-Infected Adults

Since HAART became available a decade ago, the treatment of HIV-1 infection has been streamlined. Didanosine is taken once a day and, in combinations with some other antiretroviral drugs, can be part of once-daily combination therapies. The most recent Department of Health and Human Services guidelines for the treatment of HIV-1 infection in adolescents and adults consider didanosine, in combination with lamivudine, as a good alternative nucleoside analogue backbone to be included in combination therapies for antiretroviral-naive patients.[24] Didanosine should be considered in initial treatments for patients intolerant of zidovudine, abacavir or tenofovir, as well as in combination regimens administered once daily.

In initial therapy, didanosine has been evaluated in combination with all the other nucleosides with the exception of didanosine plus zalcitabine, (for toxicity reasons), and didanosine plus abacavir (which has not yet been explored in clinical trials). Nucleoside combinations that include didanosine have been used together with protease inhibitors (indinavir, nelfinavir) and non-nucleoside reverse transcriptase inhibitors (NNRTIs; nevirapine, efavirenz). Table IV shows the characteristics of combinations that include didanosine.

Didanosine was included in twice- and three-times-daily initial regimens, usually in combination with stavudine since the advent of HAART.[47-51] As initial therapy, didanosine plus stavudine was shown to be more toxic than other combinations of nucleoside analogues,[52-54] and in particular, this combination regimen was significantly associated with increased peripheral fat loss.[54] The combination of didanosine, stavudine and abacavir had low efficacy and a high frequency of adverse events in a randomised, controlled, open-label trial performed in antiretroviral-naive patients.[55] These and other studies, as well as the description of fatal outcomes of some severe adverse events (lactic acidosis, pancreatitis), support the recommendation of not giving didanosine plus stavudine as initial therapy when other options are available.[24,56]

The advent of didanosine-EC and the possibility of administering the drug once daily has led to the evaluation of more conveniently administered and patient-friendly regimens containing didanosine.[11,57-62] Since 1998, pilot studies of once-daily triple-drug regimens have been conducted in many different countries. One of them was performed in Berlin, Germany, with intravenous drug users in the late 1990s.[57] Patients received a combination of nevirapine, lamivudine and didanosine. The study showed that 70% of patients had plasma viral loads <500 copies/mL and a CD4+ cell count increase of 150 cells/μL after 24 weeks.[57]

Since then, didanosine has been included in once-daily regimens, always in combination with lamivudine or emtricitabine, and an NNRTI. The

Table IV. Characteristics of dual-nucleoside/nucleotide combinations that include didanosine (ddI) in antiretroviral-naive patients

Combination	Pros	Cons
Highly recommended		
ddI + FTC	Convenient od regimen Potent and durable activity in clinical trials Superior to ddI + d4T in comparative trial	Only explored with EFV Not compared with other regimens (e.g. TDF + FTC)
ddI + 3TC	Convenient od regimen Highly efficacious in small, comparative trials	Minimal comparative data from clinical trials
Less recommended		
ddI + AZT	Long experience as dual NRTI therapy	No data with ddI-EC Lack of data in triple combinations (only with NVP) Inconvenient dose administration
ddI + d4T	Long experience in clinical trials Similar efficacy to other NRTI combinations (d4T + 3TC, AZT + 3TC)	Less effective than other NRTI combinations (ddI + FTC, AZT + 3TC) More mitochondrial toxicity
To be avoided		
ddI + TDF	Well tolerated, convenient od regimen	Insufficient data Concern about negative drug interaction Increased selection of resistance? Increased toxicity? Decreased CD4+ cell count?
No data		
ddI + abacavir	Well tolerated, convenient od regimen	Concern about negative drug interaction Increased selection of resistance?

3TC = lamivudine; **AZT** = zidovudine; **d4T** = stavudine; **ddI-EC** = didanosine enteric-coated capsules; **EFV** = efavirenz; **FTC** = emtricitabine; **NRTI** = nucleoside/nucleotide reverse transcriptase; **NVP** = nevirapine; **od** = once daily; **TDF** = tenofovir.

Table V. Clinical studies in which didanosine (ddI), lamivudine (3TC), emtricitabine (FTC) and efavirenz (EFV) were used as once-daily highly active antiretroviral therapy in previously untreated HIV-1-infected patients (pts)

Study	No. of pts	Type of study	Regimen	Duration (weeks)	Baseline median HIV-1 RNA (log_{10} copies/mL)	Baseline median CD4+ cell count (cell/μL)	HIV-1 RNA <50 copies/mL (%)	Mean CD4+ cell count increase (cell/μL)
Molina et al.[58]	40	Observational	ddI + FTC + EFV	24	4.77	373	93	159
Maggiolo et al.[11]	75	Observational	ddI + 3TC + EFV	48	5.09	251	77	208
Maggiolo et al.[59]	34	Clinical trial	ddI + 3TC + EFV	52	5.21	184	77.4	194
Landman et al.[60]	40	Observational	ddI + 3TC + EFV	52	5.4	164	77	199
Saag et al.[52]	286	Clinical trial	ddI + FTC + EFV	60	4.8	312	76	153
Santos et al.[61]	167	Observational	ddI + 3TC + EFV	48	4.97	142	62.9	199
Berenguer et al.[16]	186	Clinical trial	ddI + 3TC + EFV	48	5.0	205	71[a]	128[a]
DeJesus et al.[62]	65	Observational	ddI + 3TC + EFV	96	4.8	311	68	198

a Preliminary results at 24 weeks.

main randomised and non-comparative studies that assessed the efficacy and safety of didanosine, lamivudine (or emtricitabine) and efavirenz as once-daily HAART in previously untreated HIV-1-infected patients are summarised in table V.

A 24-week prospective and open-label trial evaluated the combination of emtricitabine, didanosine and efavirenz in 40 previously untreated HIV-1-infected patients. At baseline, the median HIV-1 RNA level and CD4+ cell count were 4.77 log_{10} copies/mL and 373 cells/μL, respectively.[58] The primary outcome measure was the antiretroviral effect. The viral load decreased by a median of 3.5 log_{10} copies/mL with 93% of patients achieving plasma HIV-1 RNA levels <50 copies/mL. The median increase of the CD4+ cell count was 159 cells/μL. The study treatment was generally well tolerated during the 24-week period of the study and only one patient (3%) discontinued therapy as a result of gastrointestinal intolerance. Most adverse events in this trial were mild to moderate. In summary, this study demonstrated that a once-daily combination therapy of emtricitabine, didanosine and efavirenz was well tolerated, and had potent antiviral and immunological effects.[58]

A 48-week pilot study assessed the virological and immunological efficacy of a once-daily regimen of didanosine (300 mg/day, without bodyweight adjustment), lamivudine (300 mg/day) and efavirenz (600 mg/day) in 75 consecutively enrolled antiretroviral-naive HIV-1-infected patients.[11] The proportion of patients achieving plasma HIV-1 RNA <50 copies/mL, in an intention-to-treat analysis, was 77%. Antiviral efficacy was similar in patients with baseline HIV-1 RNA level above or below 100 000 copies/mL, although patients with higher viral loads at baseline took longer to reach the 50 copies/mL threshold. The CD4+ cell count steadily increased from 251 cells/μL to 459 cells/μL. A low CD4+ cell count was a predictor of poor virological outcome. Patients with baseline CD4+ cell count <200 cells/μL showed significantly worse virological response than that observed in patients with higher baseline CD4+ cell counts.[11]

The same authors performed a randomised, open-label, controlled study with 34 antiretroviral-naive HIV-1-infected patients in each arm who received either didanosine, lamivudine and efavirenz (once-daily regimen with a low pill burden) or zidovudine and lamivudine (as Combivir®) plus efavirenz

(twice-daily regimen with a low pill burden) or Combivir® plus nelfinavir (twice-daily regimen with a high pill burden).[59] They evaluated the efficacy and tolerability of a once-daily HAART regimen compared with two other conventional twice-daily regimens. The primary outcome was the proportion of patients with viral load <50 copies/mL at week 52 of follow-up. Baseline characteristics were similar in the three groups. The proportion of patients with viral load <50 copies/mL at the end of the study was 77.4%, 77.4% and 50.0% for once-daily group, twice-daily low pill burden group and twice-daily high pill burden group, respectively.[59] Immune recovery was similar in all study arms. In summary, once-daily HAART with didanosine-EC, lamivudine and efavirenz is a well tolerated and effective alternative to twice-daily regimens.[59] This once-daily therapy, with its simple daily schedule, may be proposed as one of the first choice treatments in HIV-1 infection.

The FTC-301A study is the largest, multicentre, randomised, double-blind trial to compared emtricitabine (200 mg/day) and standard dose of stavudine as initial HAART (both in combination with didanosine-EC and efavirenz) in antiretroviral-naive HIV-1-infected patients.[52] The primary objective was to assess the efficacy and safety of both regimens. A total of 286 subjects were assigned to receive a once-daily regimen that contained didanosine, emtricitabine and efavirenz. At baseline, the median HIV-1 RNA level and CD4+ cell count were 4.8 $\log_{10}$ copies/mL and 312 cells/μL, respectively.[52] The probability of persistent virological response <50 copies/mL through to week 60 was 76% for the emtricitabine group versus 54% for the stavudine group. Patients in the stavudine group had a greater probability of an adverse event that led to study drug discontinuation (15%) than did those in the emtricitabine group (7%). The differences between treatment groups were statistically significant. In summary, once-daily emtricitabine (in combination with didanosine and efavirenz) demonstrated greater virological efficacy, durability of response and tolerability compared with a twice-daily stavudine-based combination regimen.[52]

The once-daily regimen of didanosine, lamivudine and efavirenz was demonstrated to be well tolerated and easy to administer in developing countries. In a prospective, open-label, one-arm study, 40 treatment-naive HIV-1-infected patients received the three drugs once-daily at bedtime. At baseline, the median HIV-1 RNA level and CD4+ cell count were 5.4 $\log_{10}$ copies/mL and 164 cells/μL, respectively.[60] Eighty-five per cent of patients were at Centers for Disease Control and Prevention stage B or C. The proportion of patients with plasma HIV-1 RNA <50 copies/mL at months 6, 12 and 15 were 78%, 77% and 69%, respectively. At month 15, the CD4+ cell count increased by a mean of 199 cells/μL. No permanent treatment cessations were due to severe adverse events. This study showed that this triple combination exerts strong antiretroviral and immunological effects in African patients with advanced HIV-1 infection.[60]

The VESD (Videx Epivir Sustiva once Daily) study analysed the efficacy and safety of didanosine-EC, lamivudine and efavirenz in a cohort of HIV-1-infected patients (n = 167) starting antiretroviral therapy in 2003.[61] It was a prospective, open-label, observational, multicentre study. Prior AIDS had been diagnosed in 37.7% of patients, 48.5% were co-infected with hepatitis C virus (HCV) and almost one-quarter of the population was receiving methadone therapy. Of note, 70% of patients had a CD4+ cell count <200 cells/μL and >60% had a HIV-1 RNA level >100 000 copies/mL.[61] The primary endpoint was the percentage of patients with plasma HIV-1 RNA <50 copies/mL, at week 48. Adherence was very high (90–95%) and quality of life was good or very good in 69% of patients. The proportion of patients achieving plasma viral load <50 copies/mL was 62.9% (intention-to-treat analysis) and 88.2% (on-treatment analysis), at week 48. Adverse events leading to treatment suspension were uncommon (10.7%) and tolerance of efavirenz was good in patients who took methadone, although half of the patients required dosage adjustment.[61]

A prospective open-label, randomised, clinical trial compared the non-inferiority of didanosine-EC,

lamivudine and efavirenz (once-daily, three pills a day) versus zidovudine and lamivudine (as Combivir®) plus efavirenz (twice daily, three pills a day).[16] Both regimens were administered with food in order to improve tolerability and patient convenience. The primary endpoint was the percentage of patients achieving HIV-1 RNA <50 copies/mL. At baseline, the median HIV-1 RNA level and CD4+ cell count were 5.0 $\log_{10}$ copies/mL (in both arms) and 205 and 216 cells/μL in the didanosine, lamivudine and efavirenz, and Combivir® plus efavirenz arms, respectively.[16] In an interim analysis performed at week 24, 71% and 65.9% of patients reached an HIV-1 RNA <50 copies/mL in both groups, respectively. Didanosine, lamivudine and efavirenz administered with food provided similar efficacy to that of Combivir® and efavirenz. The CD4+ cell count increase was significantly higher in the didanosine arm.[16]

In an open-label, single-arm, multicentre, prospective trial, the safety and efficacy of once-daily efavirenz, lamivudine and didanosine-EC was evaluated. Sixty-five treatment-naive patients with baseline HIV-1 RNA and CD4+ cell count of 4.8 $\log_{10}$ and 311 cells/μL, respectively, were enrolled.[62] At week 96, the proportion of patients achieving plasma HIV-1 RNA <50 copies/mL, in an intention-to-treat analysis, was 68% and the CD4+ cell count increased by a mean of 198 cells/μL.[62]

In a prospective, non-comparative study that included 70 antiretroviral-naive patients, the safety and efficacy of a once-daily regimen consisting of didanosine-EC, lamivudine and nevirapine were evaluated. The primary outcome measure was the percentage of patients with plasma HIV-1 RNA level <50 copies/mL, at 12 months in an intention-to-treat analysis.[63] At baseline, the median HIV-1 RNA level and CD4+ cell count were 5.1 $\log_{10}$ copies/mL and 262 cells/μL, respectively. At the end of follow-up, 67% of patients maintained a viral load of <50 copies/mL and CD4+ counts increased a median of 201 cells/μL. Treatment was discontinued in 18 patients, due to virological failure in 11. Most of the subjects with available genotype after virological failure showed resistance mutations to nevirapine and/or lamivudine. The treatment was more effective in patients with baseline CD4+ cell counts >100 cells/μL than in those patients with a poorer immunological status at baseline.[63]

In summary, once-daily combinations of didanosine-EC with lamivudine or emtricitabine and efavirenz (or nevirapine) have been proved to be highly efficacious as initial therapy in HIV-1-infected patients. The combination is associated with a high virological success rate and significant immunological recovery that is independent of baseline viral load. The combination is well tolerated and safely used, and little toxicity or discontinuation due to adverse events was observed in clinical studies.

2.2 Studies in Treatment-Experienced HIV-1-Infected Adults

The administration of didanosine-EC in treatment-experienced patients has been evaluated in two different contexts: patients in whom previous therapies have failed (rescue therapy) and patients with controlled viraemia who are switched to a didanosine-containing regimen for simplification purposes.

2.2.1 Studies in Virological Failure

The number of multidrug-experienced patients, as well as the time of exposure to antiretroviral drugs is increasing. As a result of consecutive treatment failures, in some experienced adults the therapeutic options for rescue or for deep salvage are very limited. NRTIs, which were the first antiretroviral agents available, are still the most frequently used drug class. Didanosine has a good resistance profile, and this fact could be an advantage to take into consideration, especially in experienced patients infected with virus with several NAMs.[40,41,43,44]

The AIDS Clinical Trial 364 (ACTG 364) evaluated the virological outcome among 104 lamivudine-experienced individuals infected with HIV-1 who switched to a didanosine-containing triple- or quadruple-drug regimen.[64] This group of patients was compared with those who continued receiving a lamivudine-containing regimen. In this retrospective study, patients switching to a didanosine-containing regimen had a significantly decreased risk

for virological failure, compared with those who continued receiving lamivudine. Didanosine continues to provide activity against viruses with the M184V/I mutation and the presence of the M184V/I mutation should not preclude the use of didanosine in nucleoside-experienced patients.[64]

Stebbing et al.[65] conducted an investigation into the concept of recycling didanosine and stavudine, with and without hydroxyurea, in the management of heavily pretreated HIV-1-infected individuals requiring salvage therapy. All existing therapy was discontinued and patients (n = 21) with treatment failure (HIV-1 RNA level >5000 copies/mL) were randomised to receive didanosine plus stavudine, or didanosine, stavudine and hydroxyurea for 12 weeks prior to optimising therapy. Significant decreases in viral load were observed during a 12-week study period, with no additional benefit of including hydroxyurea. Of note, genotypic and virtual phenotype profiles provided little additional information in this setting.[65] This small study shows that didanosine and stavudine can be efficiently recycled and are able to decrease viral load in heavily pretreated individuals.

As previously commented, a significant antiviral activity of didanosine was observed in patients infected with virus that had up to five NAMs at baseline in the Jaguar study.[40] In this subgroup of patients, the median reduction of HIV-1 RNA level was −0.45 $\log_{10}$ copies/mL in the didanosine group and +0.07 $\log_{10}$ copies/mL in the placebo group (p = 0.047). About two-thirds of patients had a history of didanosine therapy. At week 4, the proportion of patients with plasma HIV-1 RNA levels <400 copies/mL and <50 copies/mL was significantly higher in the didanosine group (31% and 11%, respectively) than in the placebo group (6% and 0%, respectively).[40] The authors concluded that in treatment-experienced patients with reverse transcriptase resistance mutations, didanosine retains significant short-term antiviral activity.

In summary, resistance to multiple drugs is common in highly treatment-experienced HIV-1-infected patients. Didanosine may still retain some or full antiviral activity when other NRTIs are no longer active.[40,43,64-67] However, fears about toxicity, especially when used in combination with stavudine, may preclude its use. Despite the alarms concerning the use of didanosine and stavudine in combination because of overlapping toxicity, there are no broad studies reflecting the magnitude of the problem in daily clinical practice. In an observational study,[68] the overall proportion of severe adverse events associated with the combination of didanosine and stavudine was low (2.9% of all patients receiving the combination), especially taking into account that the population evaluated had advanced HIV-1 infection (median baseline CD4+ cell count: 136 cells/μL; 35% had prior AIDS). The low proportion of significant adverse effects may be explained by several factors. The action taken in patients with any adverse event related to didanosine and/or stavudine was frequently the withdrawal of one or both drugs, or even the discontinuation of the whole regimen.[68] Moreover, precautionary warnings for acute pancreatitis with didanosine and stavudine, as well as other mitochondrial toxicity manifestations such as peripheral neuropathy or lactic acidosis, has meant that clinicians have a heightened awareness of monitoring of toxic effects. According to the results of this study, fear of toxicity should not preclude using didanosine plus stavudine in treatment-experienced patients who may benefit from the resistance profile of these drugs, and for whom other NRTIs may no longer be available.[68] However, it is likely that with the advent of new potent antiretroviral drugs in salvage therapy, recycling of NRTIs will become required less.

2.2.2 Switching Studies

Didanosine has been included in a simple regimen used to decrease the number of doses or pills in patients with otherwise well controlled viraemia. Combinations that included two NRTIs plus tenofovir have been evaluated for this purpose. One study investigated the treatment response in patients with previously suppressed virus (n = 55) who were switched to a two nucleoside analogues plus tenofovir regimen, mostly because previous toxicity/intolerance of original drugs.[69] At baseline, all patients had a CD4+ cell count >300 cells/μL and an

HIV-1 RNA level <50 copies/mL, for >24 weeks. Patients with a regimen including didanosine plus tenofovir had significantly poorer outcomes than those on other combinations. After 24 weeks, only 17 patients (31%) remained suppressed (HIV-1 RNA level <50 copies/mL) with the initial regimen. Multivariate analysis confirmed the combination of didanosine plus tenofovir as the only variable related to a higher rate of failure (odds ratio 17.7; 95% CI 2.1, 147; p = 0.007).[69]

In contrast with the results of switching to a regimen that included didanosine and tenofovir plus a third nucleoside analogue, a once-daily regimen containing didanosine, tenofovir and nevirapine as a simplified antiretroviral approach was successful in most patients.[70] This work assessed the long-term efficacy and safety of a once-daily antiretroviral regimen in HAART-experienced individuals with long-lasting viral suppression. A total of 169 patients with chronically suppressed viral load (limit of detection <50 copies/mL) were recruited. On the basis of patient willingness to simplify treatment, 84 continued receiving their usual treatment (twice-daily group) and 85 switched to a didanosine, tenofovir and nevirapine (once-daily group). Baseline characteristics were similar between both study groups. At week 48, a reduction in effort to take medication and an increment in the satisfaction with treatment was only seen in the once-daily group. The proportion of patients with viral suppression in the once-daily and in the twice-daily group, respectively, was 76% versus 86% in the intention-to-treat analysis (not statistically significant). Overall, adverse events leading to treatment discontinuation were more frequent in the once-daily group (mainly nevirapine-related hepatitis) than in the twice-daily group. Nevertheless, CD4+ cell count significantly decreased in the once-daily group, with a mean decline of 95 cells/μL (95% CI 45, 145). The investigators concluded that treatment simplification to a once-daily antiretroviral regimen based on didanosine, tenofovir and nevirapine may be a valid approach in HIV-1-infected individuals with long-lasting viral suppression.[70]

A once-daily regimen containing didanosine, lamivudine and efavirenz has also been evaluated as a proof-of-concept study in previously treated patients, who maintained suppression of plasma HIV-1 RNA <50 copies/mL while receiving another regimen.[71] The effects of a short-course structured intermittent therapy regimen of 7 days without antiretrovirals, followed by 7 days with once-daily administration of didanosine, lamivudine and efavirenz on plasma HIV-1 RNA levels, immunological parameters and drug toxicity were evaluated. Patients underwent laboratory evaluations every 4 weeks during the first 48 weeks of the study. All evaluations were performed after the period during which patients were not receiving antiretrovirals. Eight patients were included and in seven of them suppression of plasma HIV-1 RNA <50 copies/mL was maintained for 60–84 weeks. No 'blips' of plasma viraemia were detected during the study schedule, probably because of the long half-life of the antiretroviral drugs used. Although lamivudine and efavirenz have a low genetic barrier, there was no evidence for the emergence of resistance to the antiretrovirals drugs used.[71]

3. Tolerability and Safety: Management of Adverse Events

3.1 General Considerations: Mechanism of Toxicity

Adverse events associated with the administration of didanosine have been well known since the initial clinical trials with the drug. Gastrointestinal intolerance, peripheral neuropathy and hyperamylasaemia/pancreatitis were then most frequently reported ones. Some important conclusions were reached from these trials with the old didanosine formulation. The frequency and severity of adverse events associated with didanosine could be predicted by some factors, including advanced HIV-1 infection (CD4+ cell count <100–200 cells/μL or symptomatic HIV disease/AIDS), the presence of underlying abnormalities (previous peripheral neuropathy, hyperamylasaemia or pancreatitis), and the dose at which didanosine was administered.

Landmark studies comparing zidovudine (600 mg/day) and didanosine (400 mg/day), either as single drugs or in combination showed a similar rate of neuropathy (3.7% for zidovudine, 1.9% for didanosine and 2.3% for zidovudine plus didanosine in patients with no previous exposure to zidovudine in ACTG 175) and hyperamylasaemia (1.1% for zidovudine, 2.2% for didanosine and 2.7% for zidovudine plus didanosine in the same group of patients).[72]

In the HAART era, the rate of adverse events associated with didanosine has clearly decreased. In addition to the universal use of an optimised, weight-adjusted dose of didanosine, two other reasons may help explain the improved tolerance of the drug. Firstly, tolerability was clearly improved with the development of the enteric-coated capsule. Frequent gastrointestinal symptoms associated with the buffer used in previous formulations virtually disappeared with the new capsules. This was confirmed in a pilot study that evaluated the frequency and severity of gastrointestinal adverse events before and after switching from the buffered tablets to the enteric-coated capsules.[73] Patients were followed for 6 weeks after the change. There was a significant decrease in the rate of nausea, dyspepsia, gastrointestinal disturbance, diarrhoea and bloating. Secondly, patients are currently treated at earlier stages of HIV-1 infection with significantly better CD4+ cell counts.

However, it must be considered that new factors in current antiretroviral therapy, including a longer duration, new drugs and combinations, or drugs for associated comorbidities, could influence the tolerability and safety of didanosine. As for other antiretroviral drugs, the adverse events related to didanosine can be divided into early or late, according to the timing of development (table VI).

Mitochondrial toxicity is the most likely mechanism that explains the adverse events associated with didanosine other than gastrointestinal disturbances. Mitochondrial toxicity is shared by all the NRTIs, although the degree of mitochondrial damage varies among the different drugs.[74] Inhibition of mitochondrial γDNA polymerase by the nucleosides impairs mitochondrial DNA synthesis, leading to mitochondrial dysfunction and the subsequent clinical manifestations. There seems to be some organ specificity for the different nucleosides, with peripheral nerves and pancreas being the target organs for didanosine.

Table VI. Adverse events associated with didanosine

Early
Gastrointestinal
Peripheral neuropathy
Pancreatitis
Hyperamylasaemia
Late
Fat redistribution
Metabolic abnormalities
Lactic acidosis

3.2 Management of Early Adverse Events

3.2.1 Gastrointestinal

As stated earlier in this section, gastrointestinal disturbances are very rarely associated with the administration of didanosine since the advent of enteric-coated capsules. Clinical trials with regimens that include didanosine-EC have shown that gastrointestinal symptoms are rarely, if ever, a cause of discontinuation of the drug. Symptomatic treatment may be required in some patients for the management of potential gastrointestinal intolerance.

3.2.2 Peripheral Neuropathy

The rate of development of peripheral neuropathy has varied greatly in different studies (table VII). The frequency is higher using high dosages of the drug (daily dosages of >12.5 mg/kg) and, according to an analysis of four clinical trials, in patients with low CD4+ cell counts (<50 cells/μL) and advanced disease.[75] In this analysis, the risk of developing peripheral neuropathy appeared no greater with didanosine than with zidovudine. This led the researchers to suggest that the earlier association of didanosine with peripheral neuropathy was due to the inclusion in the studies of patients with advanced HIV-1 disease, and the use of high dosages of the drug in these studies.

Table VII. Didanosine-associated adverse events

Predisposing factors	Management
Peripheral neuropathy (frequency 1–9%)	
High dosages of didanosine	Avoid other neurotoxic drugs
Advanced HIV disease (AIDS)	Discontinue didanosine
Low CD4+ cell count (<50 cells/μL)	Drugs for pain management
Previous neuropathy	
Diabetes mellitus	
Malnutrition	
Alcohol consumption	
Other neurotoxic drugs	
Pancreatitis (0.4–7%)	
High dosages of didanosine	Avoid in patients with a history of pancreatitis
Advanced HIV disease (AIDS)	Avoid other toxic drugs
Low CD4+ cell count (<50 cells/μL)	Discontinue didanosine
History of pancreatitis	Supportive therapy
Alcohol consumption	
Hyperamylasaemia	
Hypertriglyceridaemia	
Other drugs with pancreatic toxicity	

Data with combination antiretroviral therapy in which didanosine-EC has been used confirms these results. Peripheral neuropathy is a rare occurrence in clinical trials of initial therapy. In a randomised, double-blind, controlled study, only 5% of patients receiving didanosine, emtricitabine and efavirenz developed neuropathy after a mean of 60 weeks of treatment, and <1% had to discontinue the treatment for this reason.[52] No patient taking didanosine-EC, lamivudine and efavirenz for 52 weeks developed neuropathy in another controlled study.[59] Co-administration with other potentially neurotoxic drugs may increase the risk and severity of neuropathy. Of particular interest, the combination of didanosine-EC with stavudine has been shown to be associated with a higher frequency of neuropathy (up to 13% in some studies). In an observational study including >600 heavily pre-treated patients who received didanosine and stavudine as part of a salvage regimen, approximately 5% of the patients developed neuropathy of any grade, although it was considered severe in only 0.3%.[68]

Didanosine-associated neuropathy is reversible. Management includes both preventive and therapeutic measures. Neuropathy can be minimised using adequate dosages and avoiding, when possible, the concomitant administration of other potentially neurotoxic drugs (e.g. stavudine, isoniazid, cidofovir vincristine etc.). Patients with other predisposing factors (e.g. diabetes mellitus, alcohol consumption, malnutrition etc.) may be at increased risk and the drug should be administered with caution. Identification of initial symptoms (mainly paraesthesia) is of utmost importance, since discontinuation of the drug may lead to complete reversal at early stages. Even at later stages, discontinuing didanosine is the most important measure to avoid progression and cure the existing damage. Since complete cure may take 4–12 weeks, symptomatic treatment may be necessary when pain is important (tricyclic antidepressants, carbamazepine or gabapentin may be useful).

3.2.3 Pancreatitis

Pancreatitis is a potentially serious adverse event associated with didanosine that can be fatal (<1% in early clinical trials) [table VII]. Some of the risk factors for pancreatitis are similar to those associated with neuropathy. High daily doses of didanosine, advanced HIV-1 disease and a history of pancreatitis and/or of substantial alcohol consumption have been

found to increase the risk of pancreatitis in patients with HIV-1 infection. In addition, hypertriglyceridaemia, hyperamylasaemia, and the co-administration of drugs potentially toxic for the pancreas (e.g. hydroxyurea, pentamidine etc.) may also increase the risk.

A low incidence of pancreatitis has been reported with didanosine combination therapy, even when the buffered formulation was used (0.5% in ACTG 175, equally distributed across the four treatment groups).[72] No patient receiving didanosine-EC in combination with emtricitabine and efavirenz developed symptomatic pancreatitis, and only 1 of 286 patients discontinued the drug as a result of hyperamylasaemia.[52] Overall, pancreatitis is a rare occurrence at present among patients who receive combination regimens that include didanosine and possibly not more frequent than in patients treated with other drugs.

Given the seriousness of pancreatitis it is prudent to minimise the risk of its development and to monitor patients for signs and symptoms of the disease. When possible, alternative drugs should be used in patients with either a history of pancreatitis or with hyperamylasaemia, or who must receive other potentially toxic drugs. During treatment with didanosine, changes in serum lipase and amylase levels should be monitored. Since continuation of administration of didanosine may worsen the prognosis of pancreatitis of any origin, patients should be educated in recognising symptoms of pancreatitis and getting medical advice if symptoms develop. Discontinuation of the drug is mandatory when pancreatitis is diagnosed.

3.2.4 Laboratory Abnormalities and Other Adverse Events

There are no significant or dose-limiting laboratory abnormalities associated with didanosine-EC. Increased amylase and lipase levels, without pancreatitis, can be detected, as well as increased transaminase levels without apparent clinical significance. Reversible hyperglycaemia and hyperuricaemia have also been documented in patients receiving didanosine treatment. Other infrequent adverse effects associated with didanosine treatment include optic neuritis.[76]

3.3 Management of Late Adverse Events

3.3.1 Fat Redistribution and Metabolic Abnormalities

Abnormal fat distribution has become a frequent event in HIV-1-infected patients receiving antiretroviral therapy. Although multiple factors are believed to be involved in the pathogenesis of this disorder, antiretroviral drugs seem to play a central role. Nucleoside analogue-induced mitochondrial toxicity has been clearly linked with lipoatrophy, with thymidine analogues being the most frequently associated drugs. Clinical studies have shown that patients treated for long periods with stavudine and, to a lesser extent, with zidovudine are at high risk of developing lipoatrophy.

The association between didanosine and the development of lipoatrophy has not been well established. Given the high potential for mitochondrial toxicity of didanosine, a high rate of lipoatrophy could be expected in patients receiving the drug. However, no observational study has identified didanosine as a risk factor for the development of disease. Clinical trials with the drug as initial therapy have failed to show an increased risk of developing fat abnormalities in patients receiving didanosine compared with control groups.[11,52,58,59]

The apparent lack of association between didanosine and fat abnormalities could be explained by the organ specificity for mitochondrial toxicity associated with the different nucleosides. The adipose tissue would be the target for the thymidine analogues, but not for didanosine or the other drugs in the family. As an alternative explanation, it could be argued insufficient follow-up of patients on didanosine as to have a significant incidence of lipoatrophy. Some clinical trials with the drug, however, have reported up to 3 years of follow-up.

3.3.2 Lactic Acidosis

Lactic acidosis is a rare complication of the treatment with NRTIs, although it may be severe and even fatal. It is mediated by mitochondrial toxicity

of the nucleosides and has been described with most drugs in the family. The length of administration of the drugs is the main risk factor for the development of lactic acidosis.[77]

Some cases of lactic acidosis have been described in association with didanosine, but this complication is very rare when didanosine has been administered as the only nucleoside analogue in the regimen. Most cases have occurred with a combination of didanosine and stavudine, or with didanosine given together with drugs that increase intracellular didanosine concentrations (mainly ribavirin).[34,77] The administration of stavudine plus didanosine was found to be associated with a high risk of lactic acidosis in pregnancy. For this reason, the combination of the two drugs should be avoided in pregnant women.

Lactic acidosis should be suspected in patients receiving therapy that includes nucleoside analogues who begin with nonspecific symptoms such as asthenia, gastrointestinal disturbances, myalgia, paraesthesia, dyspnoea etc. Frequent laboratory findings include abnormal liver function test and altered values of other enzymes (creatine kinase, lactate dehydrogenase, amylase etc.).[78] Metabolic acidosis with increased anion gap and increased lactate levels confirm the diagnosis. All the nucleosides should then be discontinued. Supportive therapy, frequently in intensive care units, is the mainstay of the management of the complication. No specific measures, including the administration of L-carnitine, riboflavin or thiamine, have been proved to be useful. The reinstitution of antiretroviral therapy should be carried out with caution, and NRTIs with documented toxicity should be avoided when possible. Cases of relapse of lactic acidosis after introducing nucleosides with little potential for mitochondrial toxicity have been described.[77,79]

4. Conclusion

The current formulation of didanosine as enteric-coated capsules, with all the inherent advantages, justifies the role of the drug in current antiretroviral regimens. It is reasonably well tolerated and can be conveniently administered once daily allowing its inclusion in simple once-daily HAART regimens. Recent clinical studies have suggested that didanosine-EC can be given with food together with other antiretroviral drugs, increasing the ease of administration. The efficacy of the drug has been proven as initial therapy, mainly in combination with NNRTIs. Its activity against viruses that harbour one or more thymidine-associated mutations places didanosine in a privileged position for use in treatment-experienced patients.

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References

1. BMS. VIDEX® EC (didanosine) delayed-release capsules enteric-coated beadlets. Structured product labeling [online]. Available from URL: http://www.fda.gov/cder/foi/label/2001/videxec.pdf [Accessed 2006 Oct 20]
2. Yao SY, Ng AM, Sundaram M, et al. Transport of antiviral 3′-deoxy-nucleoside drugs by recombinant human and rat equilibrative, nitrobenzylthioinosine (NBMPR)-insensitive (ENT2) nucleoside transporter proteins produced in Xenopus oocytes. Mol Membr Biol 2001 Apr-Jun; 18: 161-7
3. Alhuwalia G, Cooney D, Mitsuya H, et al. Initial studies of the cellular pharmacology of 2′,3′-dideoxinosine, an inhibitor of HIV infectivity. Biochem Pharmacol 1987 Nov 15; 36: 3797-800
4. Faulds D, Brogden RN. Didanosine a review of its antiviral activity, pharmacokinetic properties and therapeutic potential in human immunodeficiency virus infection. Drugs 1992 Jul; 44: 94-116
5. Perry CM, Balfour JA. Didanosine: an update on its antiviral activity, pharmacokinetic properties an therapeutic efficacy on the management of HIV disease. Drugs 1996 Dec; 52: 928-62
6. Perry CM, Noble S. Didanosine: an updated review of its use in HIV infection. Drugs 1999 Dec; 58: 1099-135
7. Damle BD, Kaul S, Behr D, et al. Bioequivalence of two formulations of didanosine, encapsulated enteric-coated beads and buffered tablet, in healthy volunteers and HIV-infected subjects. J Clin Pharmacol 2002 Jul; 42: 791-7
8. Damle BD, Yan JH, Behr D, et al. Effect of food on the oral bioavailability of didanosine from encapsulated enteric-coated beads. J Clin Pharmacol 2002 Apr; 42: 419-27
9. Girard P, Benech H, Gendron A, et al. Food Effect on the intracellular (IC) pharmacokinetics of dideoxyadenosine triphosphate (ddA-TP), the active metabolite of didanosine (ddI), in treated HIV-1 infected patients [poster H-1900]. 45th ICAAC; 2005 Dec 16-19; Washington DC
10. Ahluwalia G, Cooney DA, Hartman NR, et al. Anomalous accumulation and decay of 2′,3′-dideoxyadenosine-5′-triphosphate in human T-cell cultures exposed to the anti-HIV

drug 2′,3′-dideoxyinosine. Drug Metab Dispos 1993 Mar-Apr; 21: 369-76
11. Maggiolo F, Migliorino M, Maserati R, et al. Virological and immunological responses to a once-a-day antiretroviral regimen with didanosine, lamivudine and efavirenz. Antivir Ther 2001 Dec; 6: 249-53
12. Reynes J, Denisi R, Massip P, et al. Once-daily administration of didanosine in combination with d4T in antiretroviral-naîve patients: the STADI Group. J Acquir Immune Defic Syndr 1999 Sep 1; 22: 103-5
13. López JC, Moreno S, Jiménez-Oñate F, et al. A cohort study of the food effect on virological failure and treatment discontinuation in patients on HAART containing didanosine enteric-coated capsules (FOODDIe study). HIV Clin Trials 2006 Jul-Aug; 7: 155-62
14. Sánchez-Conde M, Asensi V, Sanz J, et al. Efficacy and safety of a QD regimen (didanosine, lamivudine and efavirenz) as initial therapy in HIV-infected patients [abstract WePe12.2C27]. Third IAS conference; 2005 Jul 24-27; Río de Janeiro
15. Moreno S, Antela A, Gutiérrez C, et al. A pilot, comparative study of the antiviral activity of didanosine monotherapy administered with and without food [abstract P301]. Eighth International Congress on Drug Therapy in HIV Infection; 2006 Nov 12-16; Glasgow
16. Berenguer J, Ribera E, Domingo P, et al. GESIDA 3903 team. Didanosine, lamivudine and efavirenz vs zidovudine, lamivudine and efavirenz, for initial treatment of HIV infection: planned 24-week analysis of a prospective randomized non-inferiority clinical trial, GESIDA 39/03 [abstract 504]. 14th Conference on Retroviruses and Opportunistic Infections. 2007 Feb 25-28; Los Angeles (CA)
17. Lotterer E, Ruhnke M, Trautmann M, et al. Decreased and variable systemic availability of zidovudine in patients with AIDS if administered with a meal. Eur J Clin Pharmacol 1991; 40: 305-8
18. Ruhnke M, Bauer FE, Seifert M, et al. Effects of standard breakfast on pharmacokinetics of oral zidovudine in patients with AIDS. Antimicrob Agents Chemother 1993 Oct; 37: 2153-8
19. Nazareno LA, Holazo AA, Limjuco R, et al. The effect of food on pharmacokinetics of zalcitabine in HIV-positive patients. Pharm Res 1995 Oct; 12: 1462-5
20. Ray AS, Olson L, Fridland A. Role of purine nucleoside phosphorylase in interactions between 2′,3′-dideoxyinosine and allopurinol, ganciclovir, or tenofovir. Antimicrob Agents Chemother 2004 Apr; 48: 1089-95
21. Shelton MJ, O'Donnell AM, Morse GD. Didanosine. Ann Pharmacother 1992 May; 26: 660-70
22. Damle BD, Mummaneni V, Kaul S, et al. Lack of effect of simultaneously administered didanosine encapsulated enteric bead formulation (Videx EC) on oral absorption of indinavir, ketoconazole, or ciprofloxacin. Antimicrob Agents Chemother 2002 Feb; 46: 385-91
23. la Porte C, Verweij-van Wissen C, van Ewijk N, et al. Pharmacokinetic interaction study of indinavir/ritonavir and the enteric-coated capsule formulation of didanosine in healthy volunteers. J Clin Pharmacol 2005 Feb; 45: 211-8
24. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents: a working group of the Office of AIDS Research Advisory Council (OARAC). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. October 10, 2006 [online]. Available from URL: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf [Accessed 2006 Oct 20]
25. Bruce RD, Altice FL, Gourevitch MN, et al. Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. J Acquir Immune Defic Syndr 2006 Apr; 41: 563-72
26. Kearney BP, Sayre JR, Flaherty JF, et al. Drug-drug and drug-food interactions between tenofovir disoproxil fumarate and didanosine. J Clin Pharmacol 2005 Dec; 45: 1360-7
27. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. AIDS 2005 Mar 24; 19: 569-75
28. Lacombe K, Pacanowski J, Meynard JL, et al. Risk factors for CD4 lymphopenia in patients treated with a tenofovir/didanosine high dose containing highly active antiretroviral therapy regimen. AIDS 2005 Jul 1; 19: 1107-8
29. Negredo E, Bonjoch A, Paredes R, et al. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. Clin Infect Dis 2005 Sep 15; 41: 901-5
30. Karrer U, Ledergerber B, Weber R, et al. No evidence for poor immunologic response in patients treated with a combination of tenofovir and didanosine at 250mg daily [abstract 588]. 12th Conference on Retroviruses and Opportunistic Infections; 2005 Feb 22-25; Boston (MA)
31. Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. Lancet 2001 Jan 27; 357: 280-1
32. Salmon-Ceron D, Chauvelot-Moachon L, Abad S, et al. Mitochondrial toxic effects and ribavirin. Lancet 2001 Jun 2; 357: 1803-4
33. Perronne C. Antiviral hepatitis and antiretroviral drug interactions. J Hepatol 2006; 44 (1 Suppl.): S119-25
34. Moreno A, Quereda C, Moreno L, et al. High rate of didanosine-related mitochondrial toxicity in HIV/HCV-coinfected patients receiving ribavirin. Antivir Ther 2004 Feb; 9: 133-8
35. Johnson VA, Brun-Vézinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: fall 2006. Top HIV Med 2006 Aug-Sep; 14: 125-30
36. Kozal MJ, Kroodsma K, Winters MA, et al. Didanosine resistance in HIV-infected patients switched from zidovudine to didanosine monotherapy. Ann Intern Med 1994 Aug 15; 121: 263-8
37. St Clair MH, Martin JL, Tudor-Williams G, et al. Resistance to ddI and sensitivity to AZT induced by a mutation in HIV-1 reverse transcriptase. Science 1991 Sep 27; 253: 1557-9
38. Shafer RW, Kozal MJ, Winters MA, et al. Combination therapy with zidovudine and didanosine selects for drug-resistant human immunodeficiency virus type 1 strains with unique patterns of pol gene mutations. J Infect Dis 1994 Apr; 169: 722-9
39. Winters MA, Shafer RW, Jellinger RA, et al. Human immunodeficiency virus type 1 reverse transcriptase genotype and drug susceptibility changes in infected individuals receiving dideoxyinosine monotherapy for 1 to 2 years. Antimicrob Agents Chemother 1997 Apr; 41: 757-62
40. Molina JM, Marcelin AG, Pavie J, et al. AI454-176 Jaguar Study Team. Didanosine in HIV-1-infected patients experiencing failure of antiretroviral therapy: a randomized placebo-controlled trial. J Infect Dis 2005 Mar 15; 191: 840-7
41. Marcelin AG, Flandre P, Pavie J, et al. AI454-176 Jaguar Study Team. Clinically relevant genotype interpretation of resistance to didanosine. Antimicrob Agents Chemother 2005 May; 49: 1739-44

42. Marcelin AG, Delaugerre C, Wirden M, et al. Thymidine analogue reverse transcriptase inhibitors resistance mutations profiles and association to other nucleoside reverse transcriptase inhibitors resistance mutations observed in the context of virological failure. J Med Virol 2004 Jan; 72: 162-5
43. Whitcomb JM, Parkin NT, Chappey C, et al. Broad nucleoside reverse-transcriptase inhibitor cross-resistance in human immunodeficiency virus type 1 clinical isolates. J Infect Dis 2003 Oct 1; 188: 992-1000
44. Blanco JL, Biglia A, De Lazzari E, et al. Antiretroviral activity of didanosine in patients with different clusters of reverse transcriptase mutations. AIDS 2006 Sep 11; 20: 1891-2
45. Sproat M, Pozniak AL, Peeters M, et al. The influence of the M184V mutation in HIV-1 reverse transcriptase on the virological outcome of highly active antiretroviral therapy regimens with or without didanosine. Antivir Ther 2005; 10: 357-61
46. Romano L, Venturi G, Bloor S, et al. Broad nucleoside-analogue resistance implications for human immunodeficiency virus type 1 reverse-transcriptase mutations at codons 44 and 118. J Infect Dis 2002 April; 185: 898-904
47. Eron JJ Jr, Murphy RL, Peterson D, et al. A comparison of stavudine, didanosine and indinavir with zidovudine, lamivudine and indinavir for the initial treatment of HIV-1 infected individuals: selection of thymidine analog regimen therapy (START II). AIDS 2000 Jul 28; 14: 1601-10
48. Carr A, Chuah J, Hudson J, et al. A randomized, open-label comparison of three highly active antiretroviral therapy regimens including two nucleoside analogues and indinavir for previously untreated HIV-1 infection: the OzCombo1 study. AIDS 2000 Jun 16; 14: 1171-80
49. French M, Amin J, Roth N, et al. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 infection: the OzCombo 2 study. HIV Clin Trials 2002 May-Jun; 3: 177-85
50. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. AIDS 2003 May 2; 17: 987-99
51. Sanne I, Piliero P, Squires K, et al. for the AI424-007 Trial Group. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naïve subjects. J Acquir Immune Defic Syndr 2003 Jan 1; 32: 18-29
52. Saag MS, Cahn P, Raffi F, et al. FTC-301A Study Team. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naïve patients: a randomized trial. JAMA 2004 Jul 14; 292: 180-90
53. Robbins GK, De Gruttola V, Shafer RW, et al. AIDS Clinical Trials Group 384 Team. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med 2003 Dec 11; 349: 2293-303
54. Amin J, Moore A, Carr A, et al. Combined analysis of two-year follow-up from two open-label randomized trials comparing efficacy of three nucleoside reverse transcriptase inhibitors backbones for previously untreated HIV-1 infection: OzCombo 1 and 2. HIV Clin Trials 2003 Jul-Aug; 4: 252-61
55. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. AIDS 2003 Sep 26; 17: 2045-52
56. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection. 2006 Recommendations of the International AIDS Society-USA Panel. JAMA Aug 16 2006; 296: 827-43
57. Staszewski S, Haberl A, Gute P, et al. Nevirapine/didanosine/lamivudine once-daily in HIV-infected intravenous drug users. Antivir Ther 1998; 3 Suppl. 4: 55-6
58. Molina JM, Ferchal F, Rancinan C, et al. Once-daily combination therapy with emtricitabine, didanosine, and efavirenz in human immunodeficiency virus infected patients. J Infect Dis 2000 Aug; 182: 599-602
59. Maggiolo F, Ripamonti D, Gregis G, et al. Once-a-day therapy for HIV infection: a controlled, randomized study in antiretroviral-naïve HIV-1-infected patients. Antivir Ther 2003 Aug; 8: 339-46
60. Landman R, Schiemann R, Thiam S, et al. Once-a-day highly active antiretroviral therapy in treatmen-naïve HIV-1-infected adults in Senegal. AIDS 2003 May 2; 17: 1017-22
61. Santos J, Palacios R, López M, et al. Simplicity and efficacy of a once-daily antiretroviral regimen with didanosine, lamivudine and efavirenz in naïve patients: the VESD study. HIV Clin Trials 2005 Nov-Dec; 6: 320-8
62. DeJesus E, Ward D, Cohen C, et al. Efficacy and safety of a once-daily efavirenz-based regimen for treatment naïve HIV subjects: 96-week results from the DART I Trial [abstract PE7.3/3]. Tenth European AIDS Conference/The European AIDS Clinical Society; 2005 Nov 17-20; Dublin
63. Ribera E, Rodríguez-Pardo D, Rubio M, et al. Efficacy and safety of once-daily combination therapy with didanosine, lamivudine and nevirapine in antiretroviral-naïve HIV-infected patients. Antivir Ther 2005; 10: 605-14
64. Winters MA, Bosch RJ, Albrech MA, et al. ACTG 364 study team. Clinical impact of the M184V mutation on switching to didanosine or maintaining lamivudine treatment in nucleoside reverse-transcriptase inhibitor-experienced patients. J Infect Dis 2003 Aug 15; 188: 537-40
65. Stebbing J, Nelson M, Orkin C, et al. A randomized trial to investigate the recycling of stavudine and didanosine with and without hydroxyurea in salvage therapy (RESTART). J Antimicrob Chemother 2004 Mar; 53: 501-5
66. Cozzi-Lepri A, Ruiz L, Loveday C, et al. EuroSIDA Study Group. Thymidine analogue mutation profiles: factors associated with acquiring specific profiles and their impact on the virological response to therapy. Antivir Ther 2005; 10: 791-802
67. Capdepont S, Aurillac-Lavignolle V, Faure M, et al. An additive/substractive genotypic score as a determinant of the virological response to didanosine in HIV-1 infected patients. J Clin Virol 2006 May; 36: 36-42
68. Hernández B, Moreno S, Pérez-Elías MJ, et al. Severity of the toxicity associated with combinations that include didanosine plus stavudine in HIV-infected experienced patients. J Acquir Immune Defic Syndr 2006; 15: 43: 556-9
69. Pérez-Elías MJ, Moreno S, Gutiérrez C, et al. High virological failure rate in HIV patients after switching to a regimen with two nucleoside reverse transcriptase inhibitors plus tenofovir. AIDS 2005 Apr 29; 19: 695-8
70. Negredo E, Moltó J, Muñoz-Moreno JA, et al. Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. Antivir Ther 2004 Jun; 9: 335-42
71. Dybul M, Nies-Kraske E, Dewar R, et al. A proof-of-concept study of short-cycle intermitent antiretroviral therapy with a once-daily regimen of didanosine, lamivudine, and efavirenz

for the treatment of chronic HIV infection. J Infect Dis 2004 Jun 1; 189: 1974-82
72. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. N Engl J Med 1996 Oct 10; 335: 1081-90
73. Kunches L, Einhalter N, Marquis A, et al. Tolerability of enteric-coated didanosine capsules compared with didanosine tablets in adults with HIV infection. J Acquir Immune Defic Syndr 2001 Oct 1; 28: 150-3
74. Brinkman K, Hofsted HJM, Burger DM, et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS 1998 Oct 1; 12: 1735-44
75. Kelleher T, Cross A, Dunkle L. Relation of peripheral neuropathy to HIV treatment in four randomised clinical trials including didanosine. Clin Ther 1999 Jul; 21: 1182-92
76. Lafeuillade A, Aubert L, Chaffanjon P, et al. Optic neuritis associated with dideoxyinosine. Lancet 1991 Mar 9; 337: 615-6
77. Falco V, Rodríguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficinecy virus infected patients: report of 12 cases and review of the literatura. Clin Infect Dis 2002 Mar 15; 34: 838-46
78. Lonergan J, Behling C, Pfander H, et al. Hyperlactatemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combinations regimens. Clin Infect Dis 2000 Jul; 31: 162-6
79. Lonergan JT, Barber RE, Mathews WC. Safety and efficacy of switching to alternative nucleoside analogues following symptomatic hyperlactatemia and lactic acidosis. AIDS 2003 Nov; 17: 2495-9

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