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Stavudine Once Daily

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Contents

Abstract

▲ Stavudine administered once daily is a nucleoside analogue reverse transcriptase inhibitor.

▲ The efficacy (reduction in viral load and increase in CD4+ lymphocyte counts from baseline) of stavudine once daily-containing triple therapy was similar to that of stavudine immediate release (IR)-containing triple therapy in the treatment of antiretroviral-naive patients with HIV infection in two 48-week, randomised, double-blind trials.

▲ In the largest trial (n = 783), 80% of patients receiving stavudine 75 or 100mg once daily in combination with lamivudine 150mg twice daily and efavirenz 600mg once daily, and 75% of patients receiving stavudine IR 30 or 40mg twice daily-containing combination therapy, had HIV RNA levels reduced to below the limit of quantification at 48 weeks (<400 copies/ml; intent-to-treat analysis). These findings are supported by those from the smaller trial in 150 patients.

▲ Stavudine once daily triple therapy was well tolerated, with the incidence of adverse events being similar to that with stavudine IR. Grades 2–4 treatment related adverse events occurring in ≥3% of patients in either group were dizziness, rash, abnormal dream, headache, insomnia, fatigue and peripheral neurological symptoms.

▲ Peripheral neurological symptoms occurred in 3% of patients receiving long-term treatment with stavudine once daily and 6% of patients receiving stavudine IR in a combined analysis.

Features and properties of stavudine once daily	
Indication	
HIV infection	
Mechanism of action	
Nucleoside analogue reverse transcriptase inhibitor	
Pharmacokinetic properties of stavudine 100mg once daily for 14 days (steady state)	
Peak plasma concentration (C_{max})	237.5 μg/L
Minimum plasma concentration	23.9 μg/L
Area under the plasma concentration-time curve	1746.9 μg • h/L
Time to C_{max}	3h
Apparent terminal elimination half-life	10.3h
Dosage and administration	
Usual dose in clinical trials	75mg (bodyweight <60kg) or 100mg (bodyweight ≥60kg)
Frequency of administration	Once daily
Adverse events (occurring in ≥3% of patients)	
Dizziness, rash, abnormal dream, headache, insomnia, fatigue and peripheral neurological symptoms	

Currently, highly active antiretroviral treatment regimens (HAART) [combination therapy] with various classes of antiretroviral drugs, including nucleoside analogue reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), is recommended in treatment guidelines for HIV infection.[1]

Successful treatment of HIV-infected patients depends on optimal adherence to antiretroviral therapy, which increases sustained virological control.[1] In contrast, suboptimal adherence reduces virological control, is associated with increased HIV-related morbidity and mortality and results in drug resistance, which limits therapeutic effectiveness.[1] Among other approaches (e.g. patient- or clinician-related strategies), regimen-related strategies can be employed to increase adherence to HAART, with treatment guidelines recommending simplifying regimens by minimising drug interactions and adverse effects and by reducing the number of pills and the frequency of administration.[1] Research suggests that simpler, less frequent dosing regimens may result in better compliance,[2] that patients prefer once-daily administration of antiretroviral medication,[3,4] and that pill burden has a negative impact on virological control.[5]

Stavudine (an analogue of thymidine) is among several NRTIs that are strongly recommended as components of HAART.[1] Combination therapy containing stavudine immediate release (IR) twice daily is at least as effective as other combination therapy regimens (according to virological and immunological markers of infection) in the treatment of patients with HIV infection;[6-8] it is generally well tolerated in most patients,[8,9] with adverse effects (e.g. peripheral neuropathy or lactic acidosis[10]) consistent with those associated with the NRTI class.[11] The efficacy and tolerability of stavudine twice daily have been reviewed previously in *Drugs*.[11,12]

With a move towards the simplification of antiretroviral regimens for the treatment of HIV infection aimed at improving adherence and increasing virological control, a new once-daily formulation of stavudine (stavudine once daily) has been developed. This profile presents data for the efficacy and tolerability of stavudine once daily compared with stavudine IR as a component of triple therapy for the treatment of patients with HIV infection.

1. Pharmacodynamic Profile

Detailed overviews of the pharmacodynamic profile of stavudine have been published in previous reviews in *Drugs*;[11,12] therefore, only a brief description is included in this section.

- After passive diffusion into the target cell, stavudine (a thymidine nucleoside analogue) undergoes intracellular phosphorylation to the active metabolite stavudine 5′-triphosphate,[11] which competes with thymidine 5′-triphosphate for incorporation into viral DNA by reverse transcriptase.[13] Successful incorporation causes premature termination of viral DNA chain elongation.[14]
- *In vitro*, stavudine inhibits HIV in a variety of human T cell lines; concentrations required to inhibit viral replication by 50% (IC_{50}) were generally 0.05 to 0.5 μmol/L,[15-19] with stavudine being 5- to 10-fold less potent than zidovudine in comparative trials.[18,20] Stavudine demonstrated synergistic or additive activity in combination with a range of other antiretroviral drugs, including didanosine, zalcitabine, lamivudine, nevirapine and saquinavir.[18,21] Additive or antagonistic activity has been demonstrated with stavudine combined with zidovudine *in vitro* in a zidovudine-resistant isolate.[22] Therefore, the use of stavudine in combination with zidovudine is not recommended.[10]
- In clinical trials, stavudine-containing dual or triple therapy decreased cerebrospinal fluid levels of HIV RNA to undetectable levels.[23,24] Furthermore, stavudine was associated with improved motor function and stabilised mental status in antiretroviral-naive patients with deteriorating mental function.[25] Stavudine-containing triple therapy was as effective as zidovudine-containing triple therapy at improving psychomotor performance in treatment-naive or NRTI-experienced patients with HIV infection.[26]
- Both genotypic and phenotypic resistance to

stavudine have been observed *in vitro* and *in vivo*;[11] increases in IC_{50} values of up to 12-fold (compared with baseline values[27] or a reference isolate[28]) without genotypic changes occurred in a small number of patients receiving stavudine for ≥6 months.[27,28] Mutations associated with resistance to stavudine alone are uncommon.[29] However, mutations associated with resistance to multiple NRTIs (Q151M and associated secondary mutations,[30,31] or amino acid insertions in codons 67–70[30,32]) occur in ≈1–2% of isolates, with increases in stavudine IC_{50} of 4- to >70-fold.[30-33]

- Resistance to stavudine was increased in isolates where resistance mutations to zidovudine were also present.[30,34] Stavudine monotherapy or combination therapy (often dual therapy with stavudine and didanosine) was associated with the emergence of multidrug-resistance mutations, nucleoside analogue mutations or zidovudine resistance in several studies in antiretroviral- or zidovudine-naive patients.[35-41]
- Delayed toxicities associated with dideoxynucleoside-5′-triphosphate analogues, such as stavudine, are thought to occur as a result of interference of human DNA polymerase γ, which is involved in mitochondrial DNA synthesis.[42-44] In a previous study, *in vitro* stavudine was 6-fold more potent than zidovudine at reducing mitochondrial DNA (mtDNA) content in human lymphoblastoid cells.[43] However, in more recent studies, stavudine-containing combination therapy for at least 24 weeks was associated with an increase in mtDNA.[45,46] Zidovudine and zalcitabine inhibited haemopoietic cell proliferation and differentiation in concentrations (≤10 μmol/L) at which stavudine had no significant effect, translating into a significant decrease in haemoglobin with zidovudine compared with stavudine ($p < 0.001$).[44]
- Stavudine appears to have good selectivity for HIV, with a selectivity index (the concentration required to kill 50% of human cells divided by IC_{50}) of 120–380 in most studies (values for zidovudine are higher [583–1620] indicating greater selectivity for HIV).[15-17,19,47]

2. Pharmacokinetic Profile

Data presented in this section are from studies in healthy volunteers[48] or patients with HIV infection[49,50] and were obtained from an abstract[48] or posters.[49-51]

- Mean concentration-time profiles for stavudine once daily compared with stavudine IR are presented in figure 1.[51] Pharmacokinetic data support once-daily administration of stavudine.[50,51] without regards to meals.[51] Plasma concentrations of the drug were maintained within the therapeutic range over 24 hours, with little inter- or intrapatient variability (variability in peak plasma concentrations [C_{max}], 26.5 and 9.7%; area under the plasma concentration-time curve [AUC], 31.2 and 8.3%). Asymptomatic patients with HIV infection (n = 15) received stavudine 100mg once daily (following an 8-hour overnight fast) for 9 days.[50] C_{max} and AUC were dose proportional with single doses of stavudine 37.5–100mg once daily in 25 healthy volunteers.[48]
- Drug exposure with stavudine once daily approximated that with stavudine IR after a single dose (mean AUC_{24h}, 1834.7 vs 2418.8 μg • h/L) and at steady state (1746.9 vs 2533.0 μg • h/L) in 16 antiretroviral-naive patients with HIV infection; patients received stavudine 100mg once daily or stavudine IR 40mg twice daily, both given in combination with lamivudine 150mg twice daily and efavirenz 600mg once daily, for 14 days.[49] Mean C_{max} was ≈50% lower (single dose, 187.3 vs 522.6 μg/L; steady state, 237.5 vs 520.2 μg/L)[49] and mean minimum plasma concentrations were 2–3 times higher (steady state, 23.9 vs 8.6 μg/L) [Kaul S, personal communication 2002] with the once daily formulation than with the IR formulation (figure 2). At steady state, the median time to C_{max} (t_{max}) was 3 hours with stavudine once daily and 1 hour with stavudine IR.[49]
- Neither formulation showed accumulation in the plasma after multiple doses (accumulation index, ≈1). The mean fluctuation index was reduced by almost 2-fold with stavudine once daily (2.36) compared with stavudine IR (4.23).[49]

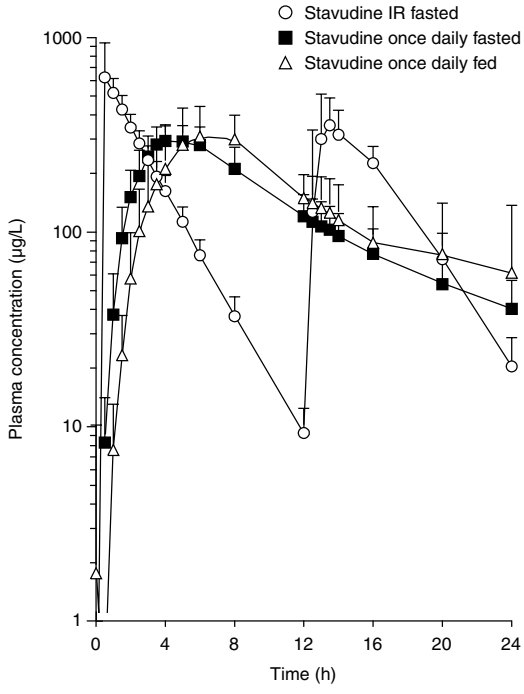

Fig. 1. Mean concentration-time profiles with two formulations of stavudine. Twenty-three healthy volunteers received stavudine IR 40mg twice daily after fasting or stavudine 100mg once daily after fasting or a high fat meal (945 kcal) in a randomised, nonblind, crossover trial.[51] Plasma concentrations were measured over 24 hours.

- On day 14, the mean terminal elimination half-life of stavudine 100mg once daily was 10.30 hours compared with 1.51 hours for stavudine IR 40mg twice daily because of prolonged absorption of stavudine once daily over 24 hours.[49] Data for stavudine IR indicate that ≈40% of an oral dose of stavudine is excreted unchanged in the urine.[10] The clearance of stavudine decreases with increasing renal impairment.[10]
- Currently, there are no data for drug-drug interactions with stavudine once daily. However, *in vitro* studies indicate that coadministration of stavudine IR and zidovudine result in lower levels of stavudine triphosphate because of competition for intracellular triphosphorylation.[52,53] This drug combination is not recommended.[10] Stavudine does not interact significantly with didanosine, lamivudine or nelfinavir.[10]

3. Therapeutic Trials

The efficacy of triple therapy with stavudine once daily has been compared with that of stavudine IR in randomised, multicentre, double-blind, double-dummy trials in 150[54] and 783[55] treatment-naive patients with HIV infection. Patients received 48 weeks' treatment with stavudine 75 or 100mg once daily or stavudine IR 30 or 40mg twice daily depending on bodyweight, with patients with bodyweight <60kg in each treatment group receiving the lower dosages.[55,56] All participants received standard lamivudine and efavirenz dosages,[55,57] reported as lamivudine 150mg twice daily and efavirenz 600mg once daily in the largest trial.[55] In

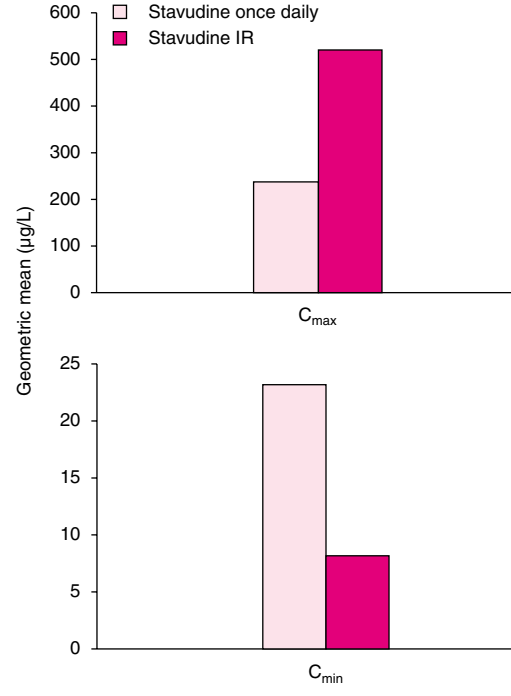

Fig. 2. Pharmacokinetics of stavudine once daily compared with stavudine immediate release (IR). Maximum and minimum plasma concentrations (C_{max} and C_{min}, respectively) at steady state (day 14) after stavudine 100mg once daily compared with stavudine IR 40mg twice daily as a component of combination therapy also containing standard doses of lamivudine and efavirenz.[49] Data are for 16 antiretroviral naive patients.

this trial (n = 783), efavirenz was substituted with nelfinavir in 23 efavirenz-intolerant patients.[55]

Treatment-naive patients (those with ≤30 days treatment of any NRTI, NNRTI or PI in the largest study[55]) with plasma HIV RNA levels ≥2000[55] or ≥5000[54] copies/ml and CD4+ counts of ≥100 cells/mm^3 (or ≥75 cells/mm^3 if no previous AIDS-defining event) were eligible for enrolment.[54,55]

Changes in plasma HIV RNA levels and CD4+ cell counts (surrogate markers of HIV infection) were used to assess efficacy.[54,55,58] The primary endpoint in the largest trial was the proportion of patients with plasma HIV RNA <400 copies/ml, with secondary efficacy criteria including the proportion of patients with plasma HIV RNA <50 copies/ml and the magnitude and durability of plasma HIV RNA and CD4+ cell changes from baseline; analyses were designed for 24[58] and 48[55] weeks. Data were reported in abstracts[54,58] and a poster.[55]

- Stavudine once daily in combination with standard doses of lamivudine and efavirenz for up to 48 weeks reduced viral loads in treatment-naive patients with HIV infection.[55,57,58] The observed virological and immunological improvements with stavudine once daily-containing combination therapy were similar to those with stavudine IR-containing combination therapy in randomised double-blind trials.[55,57,58]
- In the largest trial (n = 783), the percentage of patients with plasma HIV RNA levels below the limit of quantification (<400 copies/ml [primary endpoint] or <50 copies/ml) was similar in the stavudine 75 or 100mg once daily treatment group to that in the stavudine IR 30 or 40mg twice daily treatment group at both 24[58] and 48[55] weeks (intent-to-treat [ITT] analyses; figure 3).
- Mean reductions from baseline (median 4.8 $\log_{10}$ copies/ml) in viral RNA levels were 2.79 $\log_{10}$ copies/ml in both treatment groups at 24 weeks[58] and 2.83 and 2.86 $\log_{10}$ copies/ml in the stavudine IR and stavudine once daily treatment groups at 48 weeks.[55] At 24[58] and 48[55] weeks, CD4+ cell counts increased from baseline by a mean of 142[58] and 202[55] cells/μl, respectively, (baseline, 285 cells/μl) in patients receiving stavudine once daily and by a mean of 136[58] and 182[55] cells/μl, respectively, (baseline, 272 cells/μl) in patients receiving stavudine IR twice daily.
- In a smaller trial (n = 150),[54] 70% of patients receiving stavudine once daily-containing triple therapy and 66% of patients receiving stavudine IR-containing triple therapy had plasma HIV RNA levels of <400 copies/ml at 48 weeks; in each of these treatment groups, respectively, 41 versus 38% of patients had plasma HIV RNA levels of <50 copies/ml at 48 weeks. Viral RNA levels decreased from baseline by 2.74 and 2.64 $\log_{10}$ copies/ml, respectively, and the corresponding mean increases in CD4+ lymphocyte counts over 48 weeks were 232 and 195 cells/μl (from baseline values of 359 and 314 cells/μl).[54]

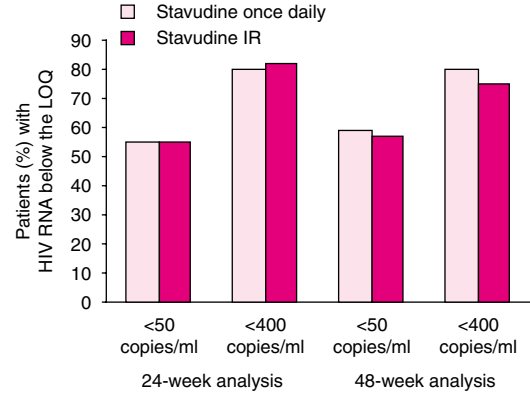

Fig. 3. Antiviral efficacy of stavudine once daily-containing triple therapy compared with stavudine immediate release (IR)-containing triple therapy in treatment-naive patients with HIV infection. Patients received stavudine 75 or 100mg once daily (n = 392) or stavudine IR 30 or 40mg twice daily (n = 391) in combination with lamivudine 150mg twice daily and efavirenz 600mg once daily in a randomised, multicentre, double-blind, double-dummy trial. Analyses were performed at 24[58] and 48[55] weeks; data are for the intent-to-treat population. **LOQ** = limit of quantification.

4. Tolerability

The tolerability of stavudine 75 or 100mg once daily in combination with lamivudine 150mg twice daily and efavirenz 600mg once daily has been compared with that of stavudine IR 30 or 40mg twice daily in combination with the same

two drugs in the larger trial described in section 3.[55,58] In addition, combined data from both the larger and the smaller trial presented in section 3 provide preliminary long-term data for combination therapy with stavudine once daily.[59]

- Triple therapy with stavudine once daily was generally well tolerated in most treatment-naive patients with HIV infection,[55,58] including patients receiving treatment for ≥1 year.[59] In the large trial, few patients (4 vs 4% for stavudine IR) discontinued treatment on or before 48 weeks because of adverse events.[55]
- The tolerability profile of HAART containing stavudine once daily was similar to that of HAART containing stavudine IR.[55,58] Overall, grades 2–4 adverse events related to treatment occurred in 30% of 392 patients receiving stavudine once daily-containing therapy and 29% of 391 patients receiving stavudine IR-containing therapy after at least 48 weeks' follow up;[55] grades 2–4 adverse events that occurred in ≥3% of patients in either treatment group included dizziness (6 vs 5%, stavudine once daily vs IR), rash (6 vs 4%), abnormal dream (3 vs 2%), headache (3 vs 2%), insomnia (3 vs 1%), fatigue (3 vs 1%) and peripheral neurological symptoms (3 vs 5%).[55] Similar adverse events, which were generally mild to moderate in severity, were reported in the smaller trial.[54]
- Many adverse events (e.g. peripheral neuropathy, lactic acidosis, pancreatitis and hepatic failure) associated with NRTIs, including stavudine, are thought to be mostly due to mitochondrial toxicity which results from the inhibition of human DNA polymerase γ (section 1).[11] The major adverse effect associated with mitochondrial toxicity during stavudine therapy is peripheral neuropathy; this effect is both dosage- and treatment duration-dependent, and most patients with mild symptoms respond to short-term cessation of treatment.[11] Grades 2–4 peripheral neurological symptoms related to therapy occurred in 3% of patients receiving stavudine once daily and 5% receiving stavudine IR for 48 weeks.[55]
- In a combined analysis, fewer patients in the stavudine once-daily treatment group experienced peripheral neurological symptoms compared with those in the stavudine IR group after long-term treatment, although the difference did not reach statistical significance (14/466 [3%] vs 28/467 [6%]).[59] In this analysis, patients received stavudine for a median of 56 weeks, although this value is driven by the cohort from the larger study and underestimates the duration of drug exposure for those from the small study who received a median of 99 weeks treatment with stavudine.[59]
- Very few patients receiving stavudine triple therapy developed hepatotoxicity, pancreatitis or symptomatic hyperlactacidaemia/lactic acidosis syndrome (<1 vs 1.5% for stavudine once daily vs IR in the larger trial[55] and <1 vs <1% in the combined analysis[59]). Lipodystrophy occurred in ≤5% of patients receiving stavudine once daily and 5% of patients receiving stavudine IR, with these results being observed both in patients receiving stavudine for a median of 56 weeks and those receiving treatment for a median of 99 weeks.[59]

5. Dosage and Administration

Stavudine once daily has been evaluated for the treatment of patients with HIV infection in two clinical trials, with dosages of 100mg once daily being administered to patients with bodyweight ≥60kg and dosages of 75mg once daily being administered to patients with bodyweight <60kg.[55,56]

6. Stavudine Once Daily: Current Status

Stavudine once daily, an NRTI, is in late-phase clinical trials for the treatment of patients with HIV infection. Triple therapy containing stavudine once daily demonstrated similar virological and immunological efficacy to triple therapy containing stavudine IR (administered twice daily). Like stavudine IR, stavudine once daily is well tolerated as a component of HAART.

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