Drugs of the Future 1998, 23(11): 1155-1167

CCC: 0377-8282/98

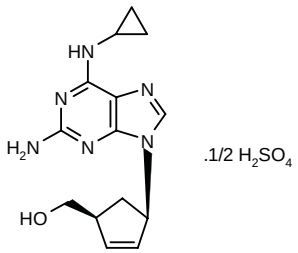
Abacavir Sulfate

Prop INNM; USAN

Anti-HIV
Reverse Transcriptase Inhibitor

1592U89 Sulfate
Ziagen™

(1*R*,4*S*)-*cis*-2-Amino-6-(cyclopropylamino)-9-[4-(hydroxymethyl)-2-cyclopentenyl]-9*H*-purine sulfate (2:1)
(1*S*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (2:1)



$C_{14}H_{18}N_6O.1/2H_2O_4S$ Mol wt: 335.3781

CAS: 188062-50-2
CAS: 136470-78-5 (as free base)
CAS: 168146-84-7 (as succinate salt)
CAS: 136777-49-6 (as dihydrochloride)
CAS: 136777-48-5 (as monohydrochloride)

EN: 173602
EN:213610 (as succinate)

Synthesis

Abacavir has been obtained by several different ways:

1) The reaction of 4,6-dihydroxypyrimidine-2,5-diamine (I) with (chloromethylene)dimethylammonium chloride (II) in refluxing chloroform gives 4,6-dichloro-2,5-bis(dimethylaminomethyleneamino)pyrimidine (III), which by reaction with aqueous HCl in hot ethanol yields monoamine (IV). The reaction of (IV) with a refluxing phosphate buffer (pH 3.2) affords *N*-(2-amino-4,6-dichloropyrimidin-5-yl)formamide (V). The condensation of (V) with (1*S*,4*R*)-4-amino-2-cyclopentene-1-methanol (VI) (1), which was obtained by optical resolution of the *cis*-racemate (VII) with D-dibenzoyltartaric acid, and elimination of the acid with ion exchange resin Amberlite IA-400 (2, 3), by means of triethylamine and NaOH in refluxing ethanol gives *N*-[2-amino-4-chloro-6-[4(*S*)-(hydroxymethyl)-2-cyclopenten-1(*R*)-ylamino]pyrimidin-5-yl]formamide (VIII). The cyclization of (VIII) with refluxing diethoxymethyl acetate (2, 3) or triethyl orthoformate (1) yields the corresponding purine derivative (IX), which is finally treated with cyclopropylamine (X) in refluxing *n*-butanol (1-3). Scheme 1.

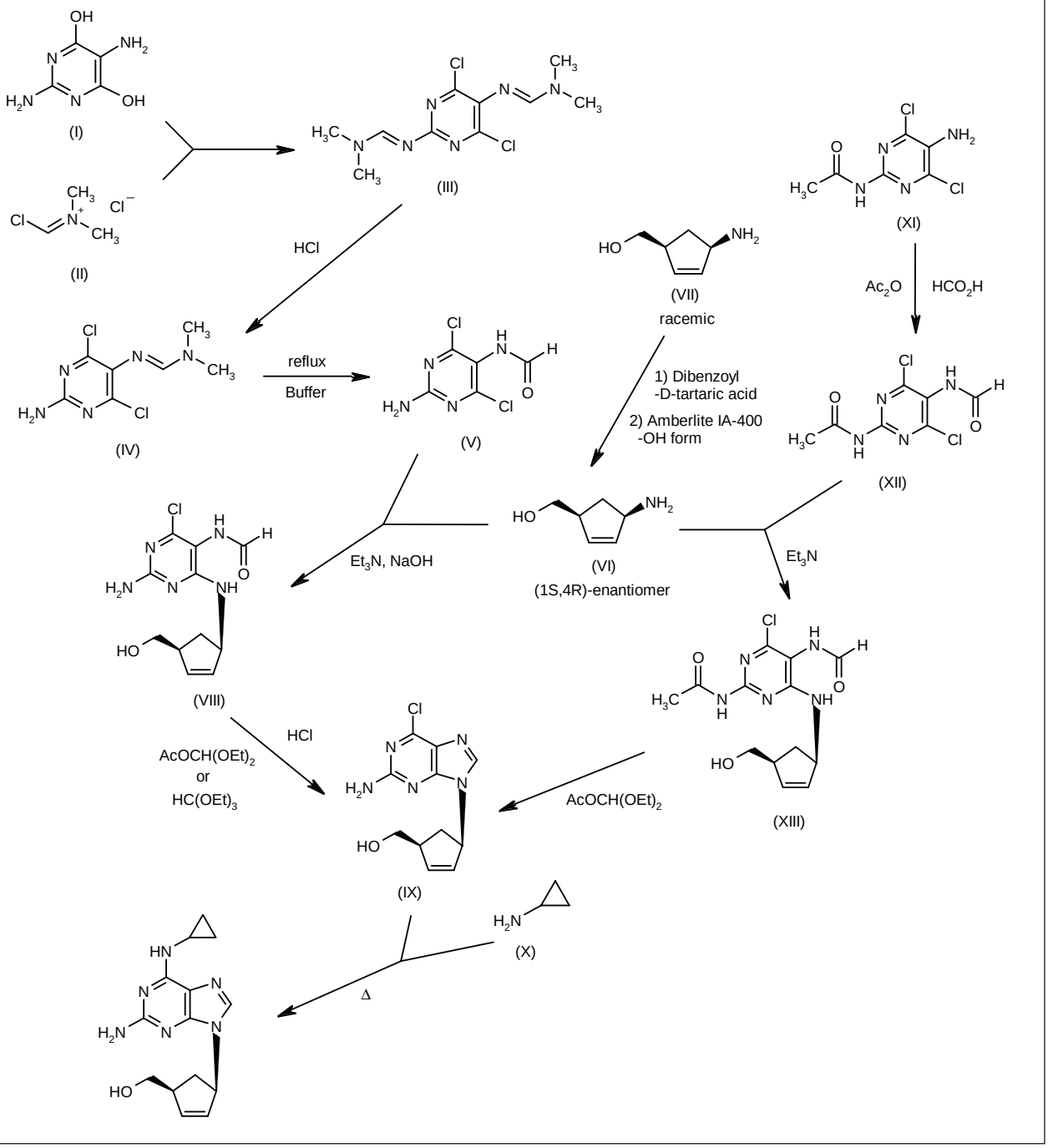
2) The formylation of *N*-(5-amino-4,6-dichloropyrimidin-2-yl)acetamide (XI) with 95% formic acid in acetic anhydride gives the expected formamide (XII), which is condensed with (1*S*,4*R*)-4-amino-2-cyclopentene-1-methanol (VI) by means of triethylamine in hot ethanol to yield the substituted pyrimidine (XIII). Finally, the cyclization of (XIII) with diethoxymethyl acetate as before affords the purine intermediate (IX) (2, 3). Scheme 1.

3) The condensation of (±)-*cis*-4-acetamido-2-cyclopentenylmethyl acetate (XIV) with 2-amino-4,6-dichloropyrimidine (XV) by means of $Ba(OH)_2$ and triethylamine in refluxing butanol gives the expected condensation product (XVI), which is treated with 4-chlorophenyldiazonium chloride (XVII) in water/acetic acid to yield the corresponding azo-compound (XVIII). The reduction of (XVIII) with Zn/acetic acid in ethanol affords the diamine (XIX), which is cyclized with refluxing diethoxymethyl acetate (XX) to afford the corresponding purine (XXI). The reaction of (XXI) with cyclopropylamine (X) in refluxing ethanol affords racemic abacavir (XXII), which is phosphorylated with $POCl_3$ giving the racemic 4'-*O*-phosphate (XXIII). Finally, this compound is submitted to stereoselective enzymatic dephosphorylation using snake venom 5'-nucleotidase (EC 3.1.3.5) from *Crotalus atrox* yielding the (–)-enantiomer, abacavir (2, 3). Scheme 2.

4) The acylation of 4(*S*)-benzyloxazolidin-2-one (XXIV) with 4-pentenoyl pivaloyl anhydride (XXV) by means of NaH in THF gives 4(*S*)-benzyl-3-(4-pentenoyl)oxazolidin-2-one (XXVI), which is submitted to a diastereoselective *syn* aldol condensation with acrolein (XXVII), using dibutylboron triflate as catalyst, affording the aldol (XXVIII). The cyclization of (XXVIII) by means of the Grubbs catalyst in dichloromethane yields the

A. Graul, P.A. Leeson, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

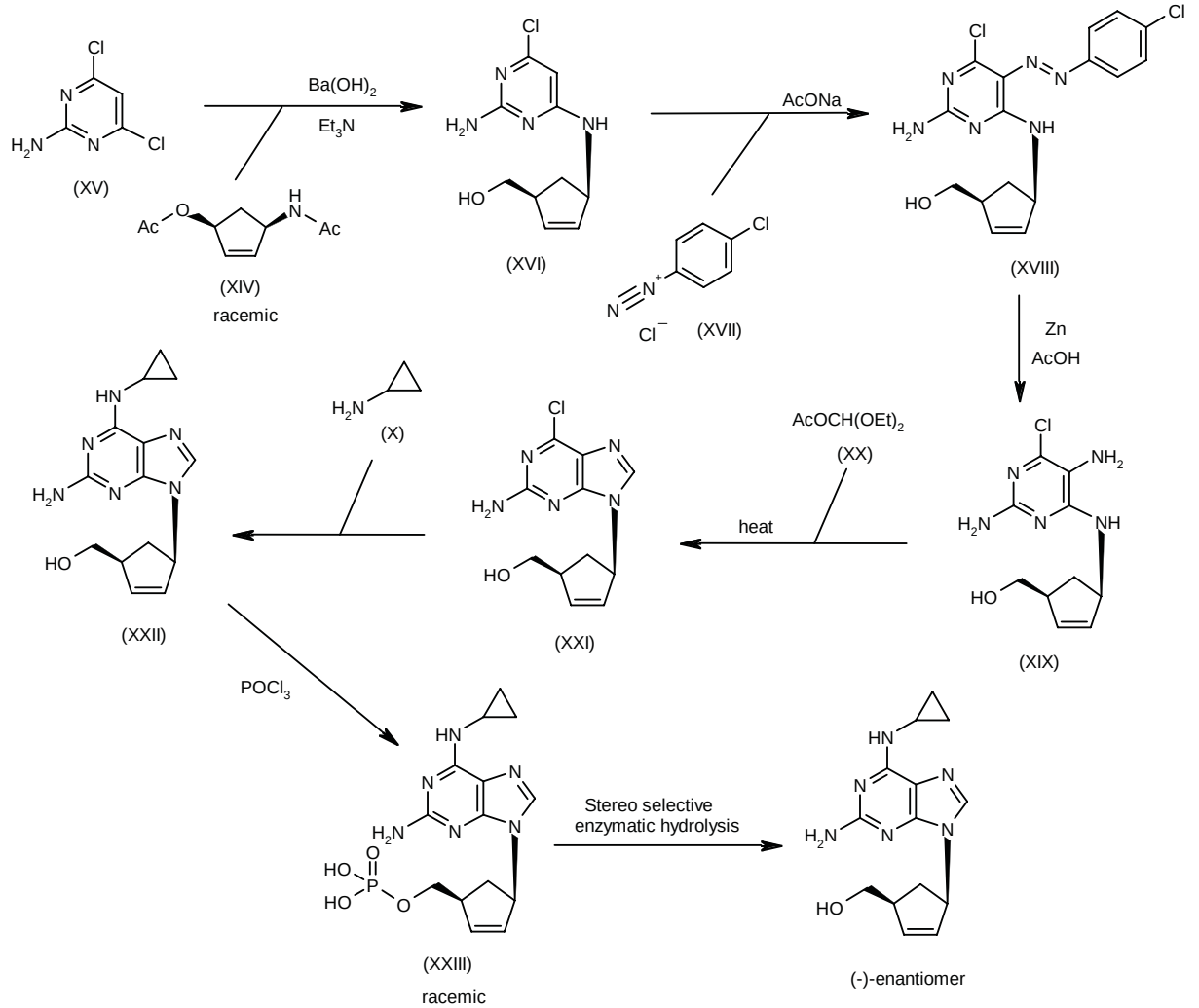
Scheme 1: Synthesis of Abacavir



cyclopentenol (XXIX), which is reduced with $LiBH_4$ in THF/methanol to give the key intermediate 5(*R*)-(hydroxymethyl)-2-cyclopenten-1(*R*)-ol (XXX). The reaction of (XXX) with methyl chloroformate/pyridine/DMAP or methyl chloroformate/triethylamine/DMAP or acetic anhydride gives the diols (XXXI), (XXXII) and (XXXIII), respectively, each of which coupled with 2-amino-6-chloropurine (XXXIV) in the presence of NaH and palladium tetrakis(triphenylphosphine) in THF/DMSO, affords the purine intermediate (IX) (4). Scheme 3.

5) The water promoted condensation of glyoxylic acid (XXXV) with cyclopentadiene (XXXVI) gives the racemic *cis*-hydroxylactone (XXXVII), which is acetylated with acetic anhydride to the acetate (XXXVIII). The selective enzymatic hydrolysis of (XXXVIII) with *Pseudomonas fluorescens* lipase yields the pure (–)-enantiomer (XXXIX),

Scheme 2: Synthesis of Abacavir



which is reduced with $LiAlH_4$ in refluxing THF, affording triol (XL). The oxidation of the vicinal glycol of (XL) with $NaIO_4$ in ethyl ether/water yields the hydroxyaldehyde (XLI), which is reduced with $NaBH_4$ in ethanol to give the key intermediate 5(*R*)-(hydroxymethyl)-2-cyclopenten-1(*R*)-ol (XXX). This compound, by reaction with triphosgene and triethylamine in dichloromethane, results in the cyclic carbonate intermediate (XXXII) (5). Scheme 4.

Description

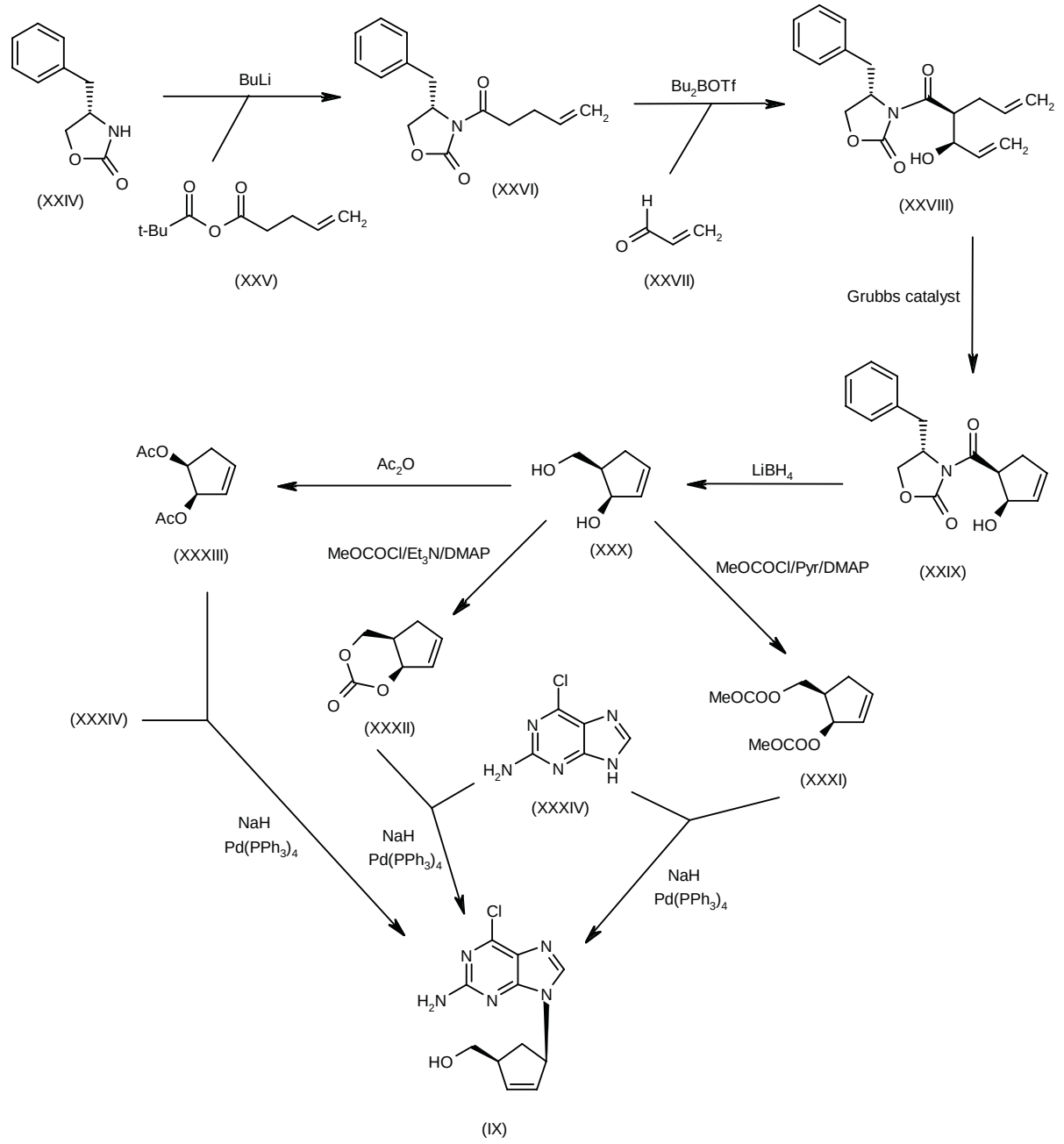
Free base: white solid foam, $[\alpha]_D^{20}$ -59.7°, $[\alpha]_{436}^{20}$, –127.8°, $[\alpha]_{365}^{20}$ –218.1° (c 0.15, MeOH) (2, 3); hydrochloride salt: off-white powder, m.p. collapses at 125-30 °C, decomposes above 138 °C, $[\alpha]_{589}^{20}$ –27.10°, $[\alpha]_{435}^{20}$ –52.3° (c 0.199, MeOH) (2); dihydrochloride salt: m.p. 176-80 °C (decomp.) (2); succinate: white powder, m.p. 168-9 °C (6).

Introduction

In spite of the many advances in the field, resulting in the introduction in recent years of several new drugs for the treatment of HIV infection and AIDS, a cure for the disease has yet to be discovered. Furthermore, existing treatment alternatives are plagued with drawbacks such as the need to follow strict dosing regimens with multiple medications, side effects and development of resistance. The need for new anti-HIV drugs, therefore, has not abated. The anti-HIV activity of several drugs that have been launched or are in development is summarized in Table II of the monograph on lodenosine, in this same issue.

In the search for new drugs to meet this need, scientists at Glaxo Wellcome synthesized a broad series of nucleoside derivatives containing the cyclopentenyl sugar mimic of (–)-carbovir, in an attempt to maximize the anti-HIV activity and improve the oral bioavailability of the compound. They found that one compound in the series, (1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol (1592U89), possessed anti-

Scheme 3: Synthesis of Intermediate (IX)

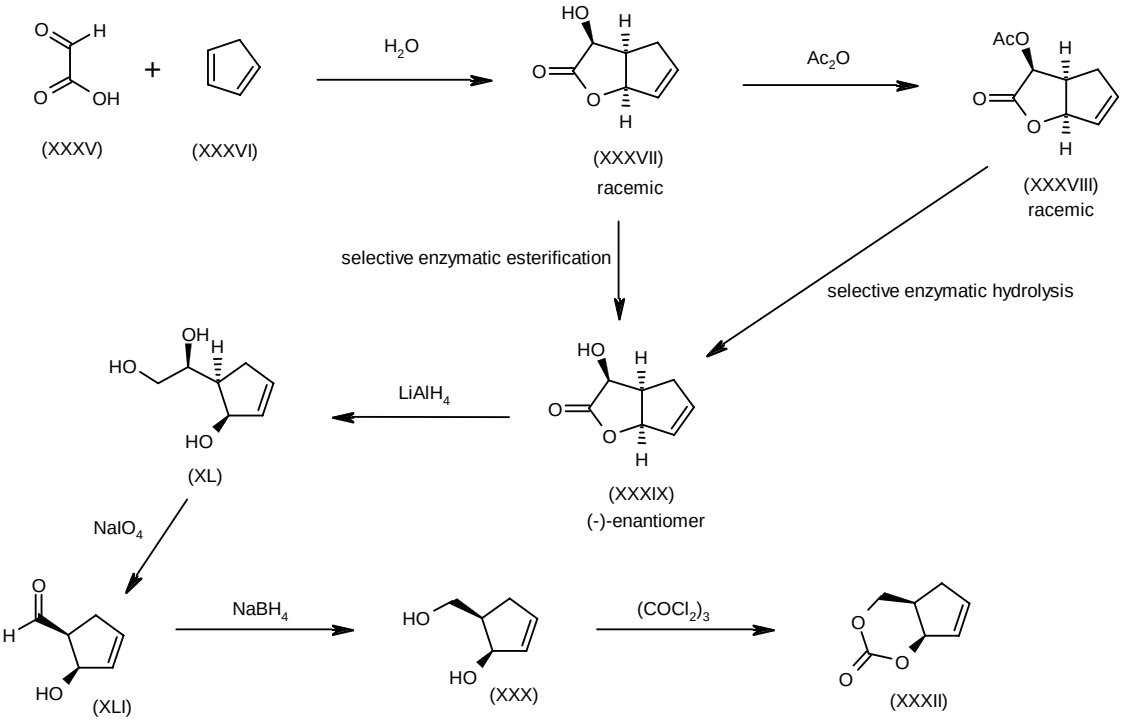


HIV activity equivalent or superior to that of zidovudine (AZT) in virus obtained from AZT-naive patients (IC_{50}s = 0.26 and 0.23 μM for 1592U89 and AZT, respectively), while having up to 100 times more potent activity than the reference compound against HIV-1(IIIB) in peripheral blood lymphocytes and MT-4 cell culture (IC_{50} = 4 μM). Furthermore, the penetration of 1592U89 into the brain and cerebrospinal fluid (CSF) was as good as that of AZT, making it potentially useful for treating the CNS manifestations of AIDS. On the basis of these early findings, including its minimal cross-resistance with AZT, 1592U89 (abacavir) was selected for further testing (7-9).

Pharmacological Actions

While the novel carbocyclic nucleoside abacavir demonstrated potent anti-HIV activity in cell lines and

Scheme 4: Synthesis of Intermediate (XXXII)



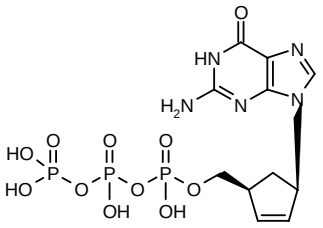
primary cultures when tested alone, even more potent activity was obtained in combination with other anti-HIV agents. In latently HIV-infected cells, the activity of abacavir was more potent than that of either zidovudine or lamivudine (3TC) in both co-culture and anti-CD3 experimental systems. The latter is a specially designed *in vitro* system in which activated cells are killed with an anti-CD25 immunotoxin to obtain a population of latently infected cells, which can then be activated with an anti-CD3 MAb or co-cultured with PHA-activated peripheral blood mononuclear cells (PBMCs) in the presence of a study drug. AZT was moderately active in the co-culture system and inactive in the anti-CD3 system, while 3TC demonstrated consistent and significant antiviral activity in both systems. The differing profiles of the three anti-HIV agents in these systems may have ramifications for the design of optimal drug combinations (10).

The efficacy of abacavir in 2- and 3-drug combinations with AZT, 3TC and stavudine (d4T) was evaluated in HIV-1-infected PBMCs. In AZT-sensitive and -resistant isolates, title compound gave IC_{50}s of 0.54 and 0.81 μM, respectively. In combination with d4T in the sensitive isolate, synergistic activity was observed at concentrations of 0.54 μM or higher. Synergistic effects were observed in combination with AZT at all concentrations tested. In combination with 3TC, synergistic activity was obtained at concentrations above the IC_{50}. Using the combination of abacavir/AZT/3TC, synergistic activity was observed in both AZT-sensitive and -resistant isolates. This particular 3-drug combination was suggested to have potential clinical utility (11).

Other *in vitro* studies demonstrated that significant synergy of anti-HIV activities was obtained with the combination of abacavir and the protease inhibitor amprenavir (141W94, VX-478) (12, 13).

The *in vivo* anti-HIV activity of abacavir, however, was even more potent than predicted from *in vitro* studies (14). This is perhaps due to the fact that the drug, following administration *in vivo*, undergoes anabolic transformation to the triphosphate form of the guanine analog (–)-carbovir, itself a potent HIV reverse transcriptase inhibitor (see Pharmacokinetics and Metabolism).

Several preclinical studies have demonstrated the favorable penetration of abacavir into the brain and CNS, a common hidden sanctuary for the virus and important reservoir for viral replication (15-18). When administered intraperitoneally to rats at the dose of 10 mg/kg, drug levels (measured 0.5-2 h postdosing) in the brain were 7-8% of those in plasma, and drug levels were maintained in this organ at or above the clinical IC_{50} level for at least 1 h. Concentrations of AZT (10 mg/kg i.p.) in the rat brain were below limits of detection 2 h postdosing, while levels of abacavir were consistently above those of AZT (0.19 μM at 2 h). Excellent penetration into the CSF was also seen in monkeys. The oral bioavailability of abacavir was 105% in rats (15).



[I]

A newly developed model of HIV-1 encephalitis in SCID mice was employed to evaluate the ability of abacavir to inhibit viral replication in the CNS. The drug, administered in two doses prior to intracerebral inoculation of the virus, resulted in a 50-80% decrease in the number of infected monocytes. Analysis of viral load in brain tissue showed a decrease of approximately 1 log in animals treated with abacavir (18, 19).

Pharmacokinetics and Metabolism

As indicated above, abacavir undergoes a process of anabolism in the body and is ultimately transformed into (–)-carbovir triphosphate (CBV-TP) [I]. This process was found to involve phosphorylation of abacavir via adenosine phosphotransferase to its 5'-monophosphate (MP) form. A novel cytosolic enzyme then converts the latter to CBV-MP, which is further phosphorylated by cellular kinases to CBV-TP. This novel activation pathway retains the potent and selective anti-HIV activity of carbovir while at the same time overcoming the pharmacokinetic and toxicity problems of the latter (20). HIV infection did not have any effect on the anabolism of abacavir to CBV-TP in $CD4^+$ CEM cells (15).

The pharmacokinetics and drug disposition of abacavir were compared to those of carbovir in rats. The pharmacokinetic profile of the title compound was clearly superior; the AUC of abacavir was 6 times greater than that of carbovir following oral dosing and its clearance was somewhat slower, while the plasma half-lives of the two compounds were similar (15).

In another pharmacokinetic study, CD-1 mice and cynomolgus monkeys were administered single oral (14 or 35 mg/kg in monkeys; 54-56 mg/kg in mice) and i.v. (14 or 35 mg/kg in monkeys; 14 or 77 mg/kg in mice) doses of abacavir. Half-life (~1.3 h), systemic clearance (~0.8 l/h/kg) and steady-state volume of distribution (~1.1 l/kg) values in monkeys were similar with both i.v. doses. After oral dosing in monkeys, peak plasma concentrations of 15 and 29 μM were observed 1.5 and 2 h after administration of the low and high dose, respectively. The absolute oral bioavailability of abacavir in monkeys was 76%. In contrast, pharmacokinetics of intravenous abacavir in mice were dose-dependent; following doses of 14 or 77 mg/kg, the respective values for half-life, clearance and volume of distribution were 0.27 and 0.78 h, 2.7 and 1.9 l/h/kg and 0.91 and 1.3 l/kg. Peak plasma levels and bioavailability of oral abacavir were also dose-dependent in mice, with respective values of 15 and 52 μM and of 92 and 76%. Administration of the [^{14}C]-radiolabeled compound to monkeys (21 mg/kg p.o.) and mice (54 mg/kg p.o.) resulted in 92 and 90% recovery of radioactivity in urine, respectively, and 7 and 21% recovery in feces, respectively. Seventy-eight percent of the radioactivity in urine was recovered in the first 8 h postadministration. In both rats and monkeys, metabolism was the primary route of elimination; only 11-13% of the drug was present in the urine as unchanged abacavir. The major metabolites in the urine – accounting for 43-52% of the dose recovered in both species – were the 5'-glucuronide and the 5'-carboxylate. (–)-Carbovir accounted for less than 2% of the dose recovered (21).

An *in vitro* hollow fiber pharmacodynamic model has been described that may be used to predict the dosage and schedule that would be appropriate for evaluation in clinical trials (22).

Toxicity

The toxicity profile of abacavir succinate was determined in rodent studies. In single-dose studies, >2000 mg/kg p.o. was determined to be the median lethal dose in CD rats, while the median LD in male and female CD-1 mice was determined to be 1730 and >1900 mg/kg, respectively. Administered by the i.v. route, the LD_{50} in both species was >260 mg/kg. Chronic administration of abacavir for 30 days in CD-1 mice (110, 220 or 1000 mg/kg/day p.o.) led to reversible elevations in serum triglyceride and cholesterol levels in females at the middle dose and in both sexes at the high dose. In monkeys administered the compound for 28 days (50, 140 or 420 mg/kg/day p.o.), liver weight increased at the highest dose and serum triglycerides became elevated in both sexes at all but the lowest dose. No other adverse events were related to abacavir dosing. In spite of its good brain penetration, abacavir did not adversely affect neurophysiological parameters in either species. No mutagenicity was seen in the Ames test. Based on this favorable toxicity profile, abacavir succinate was considered apt for clinical testing (23).

Clinical Studies

In an early phase I placebo-controlled, parallel, double-blind, dose-escalating study, abacavir tablets (100, 300, 600, 900 or 1200 mg) were administered to 18 HIV-positive volunteers with mean $CD4^+$ cell counts of 338 (range 10-713) and without significant medical conditions. Drug was administered after an overnight fast to 12 volunteers at each dose level, with at least 6 days between doses. AUC ranged from 1.07 h.μg/ml at the lowest dose to 33.12 h.μg/ml at the highest dose. C_{max} ranged from 0.59-9.61 μg/ml, while t_{max} was in the range of 1.26-

1.56 h. Half-life was 0.89 h at the lowest dose and 1.51 h at the highest dose. Six volunteers received an oral solution of abacavir in order to determine the relative bioavailability of the tablet formulation; at the dose of 300 mg, the AUC for the tablet was 99% that of the oral solution. AUC and C_{max} decreased by 5 and 35%, respectively, when drug was administered with food. Gastrointestinal disturbances were the most frequently reported adverse events, but tolerability was generally good (24).

A dose-ranging phase II study has evaluated the pharmacokinetics and antiretroviral activity of abacavir (100, 300 or 600 mg b.i.d.) monotherapy for 24 weeks, followed by open-label treatment with abacavir (300 mg b.i.d.) in combination with AZT and 3TC, in 60 patients. Interim analysis revealed viral suppression with the lowest dose, and patients were subsequently switched to the open-label arm. Pharmacokinetic analysis revealed that PK parameters were independent of dose, age, gender, body weight and combination antiretroviral therapy. Abacavir was well tolerated (25). An analysis of antiretroviral activity of abacavir in this study, with results up to the end of the 24-week monotherapy period, indicated that the compound suppressed plasma HIV-1 RNA by 17% more with the 600-mg dose than with the 300-mg dose; however, as the compound is designed to be used in combination therapy, this difference was not considered clinically relevant. Thus, the dose of 300 mg b.i.d. was recommended for phase III testing (26).

The single-dose and steady-state pharmacokinetics of abacavir, administered alone or in combination with zidovudine, were evaluated in an escalating-dose study involving HIV-positive patients. Title compound was given as monotherapy for 4 weeks, followed by an 8-week combination treatment with AZT or AZT/placebo. Both abacavir monotherapy and combination therapy with AZT were well tolerated. Viral RNA fell below limits of detection in 2/15 and 4/5 patients treated with 200 mg t.i.d. and 400 mg t.i.d., respectively, with corresponding increases in $CD4^+$ counts. Headache, nausea, asthenia and rash were the most frequent side effects, although the safety profile was generally favorable in this study (27).

HIV-positive subjects treated for 36 weeks with abacavir 300 mg q12h in addition to prescribed antiretroviral agents showed significant reductions in viral load; viral RNA was <400 copies/ml in 27/38 patients at 12 weeks and in 16/22 patients at 36 weeks. Undetectable virus was achieved in 14/18 patients on combination therapy and in 9/10 on abacavir/protease inhibitor/nucleoside combinations. The efficacy of abacavir was not affected by a 1-year interruption in treatment (28).

Eighty HIV-positive, antiretroviral-naive patients ($CD4^+$ counts $\geq$ 100; HIV-RNA $\geq$ 5000 copies/ml) were randomly treated with abacavir (300 mg q12h) in combination with one of the following protease inhibitors: indinavir (800 mg q8h), amprenavir (1200 mg q12h), saquinavir (1200 mg q8h), ritonavir (600 mg q12h) or nelfinavir (750 mg q8h). All five abacavir combinations were well tolerated, with only 4 subjects dropping out due to possible treatment-related events. Potent antiretroviral activity was observed, with viral load decreasing significantly from baseline in all treatment groups (29). Furthermore, patients treated with the abacavir combinations had significant increases in $CD8^+$ memory cells, as well as in $CD25^+$, $CD28^+$ and $CD4^+$ cells; these increases may be indicative of functional recovery (30).

As indicated above, abacavir shows excellent penetration into the brain and CNS. This was confirmed in a study in which abacavir-treated patients (600 mg q12h) were subjected to 5-6 lumbar punctures at various times after drug administration. Drug concentrations in the cerebrospinal fluid peaked in the first 2 h postdosing and declined thereafter, with an AUC for the CSF of 4.347 h.μg/l (AUC for plasma was 12.030 h.μg/l). The CNS exposure of the drug was calculated to be approximately one-third that in plasma (31).

An international, double-blind, placebo-controlled clinical study (CNAB 3001) in 99 patients with AIDS-related dementia has evaluated the therapeutic efficacy of the compound in this indication. Abacavir was administered at the dose of 600 mg b.i.d. in combination with existing anti-HIV therapy to heavily pretreated patients for 12 weeks. Lumbar puncture was performed in a subset of patients at baseline, week 6 and week 12. Genotyping and phenotyping analysis indicated a drop of more than 0.5 log during the 12-week treatment phase. Viral response was detected during preliminary analysis, although the full results of the study were not yet available at the time of reporting (32).

Abacavir has been studied most extensively in triple combination with AZT and 3TC. One phase III trial in 173 antiretroviral-naive subjects (greater than or equal to 100 $CD4^+$ cells/mm^3) has compared the efficacy of abacavir (300 mg b.i.d.)/AZT (300 mg b.i.d.)/3TC (150 mg b.i.d.) to placebo/AZT/3TC for 16 weeks. Viral RNA counts were assessed at this point, and patients with detectable virus were allowed to choose between continuing on blinded therapy, receiving open-label abacavir or discontinuing treatment with the study drugs. The study lasted for a total of 48 weeks. All study drugs were well tolerated, with only 4 patients discontinuing due to side effects. At 16 weeks, 67% of the treated patients had undetectable virus (33).

Another study in 60 treatment-naive patients (vRNA $\leq$ 30,000 c/ml and CD4 $\geq$ 100 cells/mm^3), abacavir (300 mg b.i.d.) was given alone for 24 weeks and then administered in combination with AZT/3TC; total treatment time was 72 weeks. Treatment-related adverse events included nausea and vomiting, malaise, fatigue and headache, although abacavir-containing regimens were generally well tolerated. Viral suppression was significant and prolonged. Efficacy analysis showed that following a period of monotherapy with abacavir, treatment with a combination regimen containing the compound provides significant added antiviral and immunological benefit in HIV-infected patients and represents a valuable alternative to protease inhibitor-containing regimens (34).

There is, in fact, a great deal of interest in obtaining an effective, protease inhibitor-sparing, anti-HIV regimen due to the intolerability of PIs in some patients. Patients who were already on protease inhibitors or zidovudine were switched to a "compact" triple NRTI regimen containing Combivir™ (a fixed-dose formulation incorporating 300 mg AZT and 150 mg 3TC) plus abacavir (300 mg). Preliminary data from the ongoing study, presented at a meeting earlier this fall, indicate that beneficial immunologic and virologic results are being obtained, with decreases in viral load from 1367 c/ml at week 1 to 58 c/ml at week 8 (35).

Promising results have also been obtained with abacavir in combination with the protease inhibitor amprenavir. An early pharmacokinetic study evaluated the potential interactions between the two antiretroviral drugs, and established a lack of negative interaction at the doses of 900 mg b.i.d. amprenavir and 300 mg b.i.d. abacavir (36).

A combination study planned to enroll 50 patients (40 enrolled at time of interim reporting) is testing the drugs in combination at the dose of 300 mg b.i.d. abacavir and 1200 mg b.i.d. amprenavir for a period of 72 weeks. Data obtained with up to 24 weeks of treatment have been presented. Viremia at week 20-24 was below the limits of detection using a boosted Amplicor assay (limit of detection: 5 copies/ml) in 3 of 11 patients, <5 copies/ml in 6 of 11 and <50 copies/ml in 9 of 11 patients. After 24 weeks of treatment, the percentages of $CD4^+$ and $CD8^+$ cells in the lymph nodes of amprenavir/abacavir-treated patients were similar to those in healthy controls, indicating normalization of the $CD4^+/CD8^+$ ratio. Side effects of the combination included rash (causing 2 patients to discontinue threapy), nausea, diarrhea, epigastric pain and headache (37, 38).

Promising findings with abacavir/AZT/3TC and abacavir/amprenavir combinations led to the evaluation of the four drugs together, administered twice daily to acutely or chronically HIV-infected patients not previously treated with 3TC or protease inhibitors. Thirteen acutely and 12 chronically infected subjects were enrolled and treated with abacavir (300 mg), amprenavir (1200 mg) and Combivir™ (AZT/3TC; 300 mg/150 mg); the study had been in progress for 7 months at the time of reporting. Nausea, vomiting, fatigue and rash were the most frequent side effects. Plasma HIV RNA was below limits of detection (<100 copies/ml) after 8, 12 and 20 weeks of therapy in 14/20, 8/12 and 5/8 patients, respectively. Viral RNA in CSF decreased by 1.22 log after 3-8 weeks of treatment. $CD4^+$ counts increased by 172 and 126 cells/μl in acutely and chronically infected patients, respectively, at 12 weeks. Viral suppression with this four-drug cocktail was prompt and sustained (39).

Abacavir has also been studied quite extensively in pediatric patients. A phase I study in patients with a median age of 6.7 years involved discontinuation of previous antiretroviral therapy and then either 6 weeks of abacavir at 4 mg/kg b.i.d. followed by 6 weeks of drug at 8 mg/kg b.i.d., or 12 weeks of abacavir at 8 mg/kg b.i.d. After 12 weeks of monotherapy, subjects were randomized to abacavir (8 mg/kg b.i.d.) plus a second antiretroviral agent (AZT, d4T, ddI or 3TC). Thirty-nine children began the trial; 2 were removed due to toxicity during the monotherapy treatment stage. Possible treatment-associated neuropenia was detected in 3 children during the second part of the study. Six or 12 weeks after discontinuing prior therapy and initiating treatment with abacavir, no changes in $CD4^+$ count or plasma HIV RNA concentrations were observed. Further studies were reportedly in progress with the objective of studying efficacy, but this study showed that short-term treatment with abacavir in children is associated with good tolerability and safety (40).

Another interim report showed that combination therapy in HIV-infected children with AZT/3TC, with or without added abacavir, leads to reductions in viral load in the CSF, indicating the potential usefulness of the compound in the treatment of HIV encephalopathy in children. Twenty-four antiretroviral-experienced children (aged 1-10 years) were randomized to treatment with AZT/3TC or AZT/3TC/abacavir. Samples of CSF were taken at baseline and after 8 weeks of therapy. At baseline, 79% of the subjects had abnormal neurological findings and 67% had severe encephalopathy. HIV-1 RNA decreased significantly upon initiation of drug therapy, from a level of 2534 copies/ml at week 0 to <100 copies/ml at week 8. Concentrations of the cytokine MIP-α were below 15 pg/ml in all samples of CSF evaluated. MCP-1 levels in CSF samples also decreased, although not significantly. Viral RNA in the CSF did not correlate significantly with concentrations of the cytokines MCP-1, MIP-α or TNF-α and with findings of encephalopathy in this treatment group. While both antiretroviral combinations appear to be effective in this population, more accurate markers of CNS disease severity in children are needed (41, 42).

A phase III pediatric study has evaluated the safety and anti-HIV efficacy of the abacavir/AZT/3TC cocktail and compared it to that of AZT/3TC in 205 treatment-experienced children. At time of reporting, 135 children had been treated for at least 16 weeks. Abacavir was well tolerated by the children in this study, with only 2 patients withdrawing due to hypersensitivity to the drug. Data analysis will be available at a later date, but early indications are that abacavir will be a valuable addition to the limited treatment options available for pediatric AIDS patients (43).

Box 1 summarizes the results of clinical studies on abacavir.

The safety of abacavir in clinical studies has been, in general, quite good. A global analysis of 171 patients treated with the drug in phase II trials indicated that the most common reason for discontinuing treatment is a hypersensitivity reaction, occurring in about 3% of all patients. It is essential that patients manifesting this syndrome not be reexposed to the drug. Grade III and IV laboratory abnormalities have been rare with abacavir, and are usually attributable to other drugs administered in combination with the compound (44). No adverse interactions have been seen in HIV-infected subjects taking abacavir in combination with ethanol (45).

Box 1: Summary of clinical studies on abacavir.

Study Design	Population	Treatment	Results	Ref.
Double-blind, parallel, placebo-controlled, dose-escalation phase I trial	18 HIV+ volunteers (15 male)	100, 300, 600, 900 and 1200 mg with at least 6 days between doses	ABC was safe and well tolerated. Few adverse events, usually GI disturbances.	24
Randomized, blinded, dose-ranging phase II trial	60 HIV-1 infected patients	100, 300, 600 mg BID x 24 wk	ABC was well tolerated. Insufficient viral load suppression with 100 mg BID. 300 mg BID selected for phase III efficacy trials.	25, 26
Blinded, dose escalating protocol	HIV-infected adult male and female patients	200 mg TID, 400 mg TID, 300 mg BID, 600 mg TID x 4 wk followed by 8 wk of ZDV or placebo	There was a marked reduction of viral load (measured by HIV-RNA PCR) by ABC monotherapy and combination therapy with ZDV. Well tolerated.	27
Randomized, open-label	80 antiretroviral naive HIV-infected adult subjects	300 mg/12 h ABC in combination with one of the following PIs: -amprenavir 1200 mg/12h -indinavir 800 mg/8h -ritonavir 600 mg/12 h -saquinavir 1200 mg/8 h -nelfinavir 750 mg/8 h	ABC was well tolerated in dual combination with five different HIV protease inhibitors showing strong antiretroviral activity. These regimens increased selected T-cell subpopulations with exception of $CD8^+$ memory cells. Functional recovery may be predicted by $CD25^+$ and $CD28^+$ $CD4^+$ cells increases.	29, 30
Randomized, double-blind	99 patients with AIDS dementia complex	Current therapy + abacavir 600 mg BID or placebo x 12 wk	Preliminary results show a viral load response in ~ 25% of patients. ABC 600 mg BID effects in experienced patients not yet available.	32
Randomized, double-blind phase III trial	173 HIV-infected subjects	3TC 150 mg BID + ZDV 300 mg BID in combination with ABC 300 mg BID or placebo	ABC was well tolerated. Plasma HIV-1 RNA level below the detection limit of the assay (400 copies/ml) at week 16 in most of participants receiving combination nucleoside therapy.	33
Open label	55 antiretroviral therapy naive patients	ABC 300 mg BID + 3TC/ZDV x 72 wk	Triple nucleoside therapy with ABC achieved a wide extent and a long-term durability of viral suppression and immunologic response. There was also a good safety profile.	34
Open-label prospective	40 HIV-1 infected subjects	ABC 300 mg p.o. BID + amprenavir 1200 mg p.o. BID x 72 wk	This combination therapy was well tolerated, effectively suppressed HIV-1 replication, induced a normalization of the CD4/CD8 ratio in the peripheral blood and restored $CD4^+$T cells in lymph nodes.	37
Phase II trial	Subjects acutely and chronically infected	ABC 300 mg + 141W94 1200 mg + AZT/3TC 300/150 mg BID	After 17 weeks, this 4-drug BID regimen has been shown to be safe and well tolerated. There has been a prompt and sustained suppression of plasma viral load in all participants.	
	26 HIV-infected children	3TC/ZDV alone or + ABC	3TC/ZDV reduced CSF viral load. Addition of ABC resulted in greater viral load suppression than seen with ZDV/3TC alone.	41
Blinded, randomized, phase II trial	205 HIV-infected children	3TC/ZDV alone or + ABC x 16 wk	ABC was well tolerated and preliminary results showed ABC to be a valuable addition to treatment options available for pediatric AIDS.	43

Source: Prous Science CTLine database.

Viral resistance to anti-HIV drugs is a common problem, and the potential for development of abacavir-resistant mutants has therefore been evaluated. *In vitro* selection studies were performed with the objective of generating abacavir-resistant variants of wild-type and AZT-resistant HIV-1. Two or three mutations were required in order for the virus to develop significant resistance to abacavir, with approximately 10-fold maximum increases in IC_{50}s. The mutations identified at the reverse transcriptase coding region were 65R, 74V, 184V and 115F. In the presence of only a single mutation at any of these sites, susceptibility decreased by no more than 2- to 3-fold, suggesting a low potential for rapid high-level resistance in the clinic. In clinical studies, the mutations at codons 65, 74 and 184 developed in some patients undergoing monotherapy with abacavir during 12 weeks. Administration in combination with AZT appeared to prevent the development of said mutations. Other studies showed some evidence of cross-resistance with zalcitabine and didanosine, as well as high-level resistance with 3TC. No cross-resistance was seen with d4T or AZT. Testing with the Antivirogram™ method has been suggested in order to predict response to abacavir therapy and to identify patients who are most likely to benefit from treatment with the compound (46-49).

In June 1998, Glaxo Wellcome filed for regulatory approval of both pediatric and adult dosage forms of abacavir sulfate (Ziagen™) in the U.S. and European Union. On November 3, the FDA Antiviral Drugs Advisory Committee recommended accelerated approval of the compound (50).

Manufacturer

Glaxo Wellcome (UK).

References

1. Daluge, S.M., Martin, M.T., Fugett, M.J.F. (The Wellcome Foundation Ltd.). *Chloropyrimide intermediates.* WO 9521161.

2. Daluge, S.M. (The Wellcome Foundation Ltd.). *Therapeutic nucleosides*. EP 434450, JP 96092252.

3. Daluge, S.M. (Burroughs Wellcome Co.). *Therapeutic nucleosides.* AU 8937025, EP 349242, JP 90045486, US 5034394, US 5089500.

4. Crimmins, M.T., King, B.W. *An efficient asymmetric approach to carbocyclic nucleosides: Asymmetric synthesis of 1592U89, a potent inhibitor of HIV reverse transcriptase.* J Org Chem 1996, 61: 4192-3.

5. Olivo, H.F., Yu, J. *Practical enantiodivergent syntheses of both enantiomers of carbovir, 1592U89 and six-membered ring analogues.* J Chem Soc Perkin Trans 1998, (3): 391-2.

6. Daluge, S.M., Wilson, J.D. (The Wellcome Foundation Ltd.). *4-(2-Amino-6-(cyclopropylamino)-9H-purin-9-yl)-2-cyclopentene-1-methanol succinate as antiviral agent.* JP 98505593, WO 9606844.

7. Daluge, S.M., Good, S.S., Faletto, M.B., Martin, M.T., Miller, W.H., Averett, D.R., St. Clair, M.H., Boone, L.R., Tisdale, M., Reardon, J.E. *1592U89 succinate – A potent, selective anti-HIV carbocyclic nucleoside.* Antivir Res 1995, 26(3): Abst 7.

8. Tisdale, M., Parry, N.R., Cousens, D., St. Clair, M.H., Boone, L.R. *Anti-HIV activity of (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (1592U89).* 34th Intersci Conf Antimicrob Agents Chemother (Oct 4-7, Orlando) 1994, Abst I82.

9. Daluge, S.M., Good, S.S., Martin, M.T., Tibbels, S.R., Miller, W.H., Averett, D.R., St. Clair, M.H., Ayers, K.M. *1592U89 succinate – A novel carbocyclic nucleoside analogue with potent, selective anti-HIV activity.* 34th Intersci Conf Antimicrob Agents Chemother (Oct 4-7, Orlando) 1994, Abst I6.

10. Saavedra, J., Johnson, C., Koester, J., St. Clair, M., Vitetta, E., Ramilo, O. *Comparative antiviral effect of zidovudine (ZDV), lamivudine (3TC) and 1592U89 on latently HIV-infected cells.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 29-Oct 1, Toronto) 1997, Abst I-59.

11. Tremblay, C., Merrill, D.P., Chou, T.C., Hirsch, M.S. *1592U89 as a component of 2- and 3-drug regimens against zidovudine-sensitive and zidovudine-resistant HIV isolates in vitro.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 632.

12. Drusano, G.L., D'Argenio, D.Z., Symonds, W., Bilello, P.A., McDowell, J., Sadler, B., Bye, A., Bilello, J.A. *Nucleoside analog 1592U89 and human immunodeficiency virus protease inhibitor 141W94 are synergistic in vitro.* Antimicrob Agents Chemother 1998, 42: 2153-9.

13. Ravitch, J.R., Bryant, B.J., Reese, M.J., Boehlert, C.C., Walsh, J.S., McDowell, J.P., Sadler, B.M. *In vivo and in vitro studies of the potential for drug interactions involving the anti-retroviral 1592 in humans.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 634.

14. Daluge, S.M., LaFon, S.W., Good, S.S., St. Clair, M.H., Livingston, D.A., Martin, M.T. *Anti-HIV agent 1592U89 succinate – Progress from synthesis through clinical development.* Antivir Res 1996, 30(1): Abst 2.

15. Daluge, S.M., Good, S.S., Faletto, M.B. et al. *1592U89, a novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity.* Antimicrob Agents Chemother 1997, 41: 1082-93.

16. Thomas, S., McDowall, J.E., Cheah, V., Bye, A., Segal, M.B. *The entry of 1592 (abacavir) into the guinea-pig brain: Comparison with other reverse transcriptase inhibitors.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 41192.

17. Ravitch, J.R., Jarrett, J.L., White, H.R., Polli, J.W., Humphreys, J.E., Good, S.S. *CNS penetration of the anti-retroviral 1592 in human and animal models.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 636.

18. Limoges, J., McClernon, D.R., Persidsky, Y., Rasmussen, J., Lanier, E.R., Reinhard, J., Gendelman, H.E. *Abacavir (1592, ABC) prevents spread of HIV-1 in brain tissue of SCID mice with HIV-1 encephalitis.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 11233.

19. Limoges, J., Persidsky, Y., Rasmussen, J., Lanier, R., Reinhard, J., Gendelman, H.E. *1592 prevents viral spread in brain tissue of SCID mice with HIV-1 encephalitis.* 5th Conf

Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 635.

20. Faletto, M.B., Miller, W.H., Garvey, E.P., St. Clair, M.H., Daluge, S.M., Good, S.S. *Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89.* Antimicrob Agents Chemother 1997, 41: 1099-107.

21. Good, S.S., Owens, B.S., Faletto, M.B., Mahony, W.B., Domin, B.A. *Disposition in monkeys and mice of (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (1592U89) succinate, a potent inhibitor of HIV.* 34th Intersci Conf Antimicrob Agents Chemother (Oct 4-7, Orlando) 1994, Abst I86.

22. Bilello, J.A., Bilello, P.A., Symonds, W., McDowell, J., Drusano, G.L. *1592U89 a novel carbocyclic nucleoside inhibitor of reverse transcriptase limits HIV replication in an in vitro hollow fiber pharmacodynamic model.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst I-67.

23. Ching, S.V., Ayers, K.M., Dornsife, R.E., Grebe, G.L., Howard, J.L. *Nonclinical toxicology and in vitro toxicity studies with the novel anti-HIV agent (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (1592U89) succinate.* 34th Intersci Conf Antimicrob Agents Chemother (Oct 4-7, Orlando) 1994, Abst I88.

24. McDowell, J.A., Symonds, W.T., Kumar, P.N., Sweet, D.E., Blum, M.R., Lafon, S. *Initial phase I study of anti-HIV agent 1592U89 in a single-dose escalation design including food effect and dosage form evaluation.* 35th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, San Francisco) 1995, Abst I109.

25. Weller, S., Radomski, K.M., Lou, Y., Stein, D.S. *Abacavir (1592, ABC) population pharmacokinetics (PK) from a phase II dose-ranging trial in HIV-1-infected adults.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst A-68.

26. Weller, S., Muir, K., Stein, D.S. *Abacavir (1592, ABC) pharmacokinetics/pharmacodynamics (PK/PD) from monotherapy dosing in antiretroviral naive HIV-1-infected patients.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst A-69.

27. Saag, M., Lancaster, D., Sonnerborg, A. et al. *Preliminary data on the safety and antiviral effect of 1592U89, alone and in combination with zidovudine (ZDV) in HIV-infected patients with CD4+ counts 200-500/mm^3.* 11th Int Conf AIDS (July 7-12, Vancouver) 1996, Abst Th.B.294.

28. Torres, R., Saag, M., Lancaster, D. et al. *Antiviral effects of abacavir (1592) following 36 weeks of therapy.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 659.

29. Mellors, J., Lederman, M., Haas, D. et al. *Antiretroviral effects of therapy combining abacavir (1592) with HIV protease inhibitors (PIs).* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 4.

30. Lederman, M., Mellors, J., Haas, D., Horton, J., Haubrich, R., Stanford, J., Cooney, E., Donnenberg, A., Neisler, M., Kelleher, D. *Early T-lymphocyte responses to antiretroviral therapy with abacavir (1592) and HIV protease inhibitors (PIs).* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 364.

31. Price, R.W., Aweeka, F., Bellibas, S.E., Staprans, S., Novakovic-Agopian, T., Mahoney, W., Symonds, W. *Pharmacokinetics of abacavir (1592U89) in cerebrospinal fluid (CSF) using multiple lumbar punctures of few subjects and "sparse sampling" techniques.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 42271.

32. Lanier, R., McArthur, J., Atkinson, J.H., Price, R., Clifford, D., Simpson, D., Torres, G., Sturge, G. *Viral resistance and viral load response to abacavir (ABC, 1592) in an AIDS dementia complex trial (CNAB 3001).* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 32293.

33. Fischl, M., Greenberg, S., Clumeck, N., Peters, B., Rubio, R., Pobiner, B., Verity, L. *Safety and activity of abacavir (1592, ABC) with 3TC/ZDV in antiretroviral naive subjects.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12230.

34. Staszewski, S., Katlama, C., Harrer, T., Massip, P., Yeni, P., Cutrell, A., Steel, H.M. *Abacavir (1592, ABC) in protocol CNAB 2002, provides effective, long-term, 72 week, ART for patients on triple therapy regimens.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12212.

35. Henry, K., Shaeffer, M.S., Bellman, P., Norris, D., Wallace, R., Sawyer, G. *TARGET: Preliminary data of effective switch/intensification treatment with Combivir™ and Ziagen™ in therapy-experienced adults.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-98.

36. McDowell, J.A., Sadler, B.M., Millard, J., Nunnally, P., Mustafa, N. *Evaluation of potential pharmacokinetic (PK) drug interaction between 141W94 and 1592U89 in HIV+ patients.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst A-62.

37. Bart, P.-A., Rizzardi, G.P., Gallant, S., Meylan, P., Spreen, W., McDade, H., Pantaleo, U.K. *Combination abacavir (1592, ABC)/amprenavir (141W94) therapy in HIV-1 infected antiretroviral naive subjects with CD4$^+$ counts > 400 cells/μl and viral load > 5000 copies/ml.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12204.

38. Bart, P.-A., Rizzardi, G.P., Gallant, S. et al. *Combination 1592/141W94 therapy in HIV-1 infected antiretroviral naive subjects with CD4$^+$ counts > 400 cells/μl and viral load > 5000 copies/ml.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 365.

39. Kost, R., Cao, Y., Vesanen, M. et al. *Combination therapy with abacavir (1592), 141W94, and AZT/3TC in subjects acutely and chronically infected with HIV.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 363.

40. Kline, M.W., Blanchard, S., Shenep, J.L. et al. *A phase I study of 1592U89 in HIV-infected children.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 269.

41. Saez-Llorens, X., Castrejon Alba, M.M., Guerra, E.C., McClemon, D.R., Gilbert, C.A., McCoig, C.C., Ramilo, O. *3TC/ZDV ± abacavir (ABC) reduces CSF viral load in HIV-infected children (CNA3006).* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12252.

42. Castejon, M., McCoig, C., McClernon, D., Danehower, S., Lanier, R., Gilbert, C., Keller, A., Castano, E., Saez-Llorens, X. *Impact of treatment with zidovudine (ZDV)/lamivudine (3TC) OM abacavir (ABC) on cerebrospinal fluid (CSF) HIV-1 RNA and cytokine concentrations in HIV-1-infected children.* 38th Intersci

Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-8.

43. Van Dyke, R., Saez-Llorens, X., Nelson, R.P., Emmanuel, P., Wiznia, A., Gilbert, C.A., Keller, A. *Antiretroviral activity and safety of abacavir (1592, ABC) with 3TC/ZDV in therapy-experienced children.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12255.

44. Hetherington, S., Steel, H.M., Lafon, S., Spreen, W., Pearce, G. *Safety and tolerance of abacavir (1592, ABC) alone and in combination therapy of HIV infection.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12353.

45. McDowell, J., Pilati-Stevens, T., Lou, Y., Edwards, K., Kelly, E., Yuen, G.J. *Evaluation of the pharmacokinetic (PK) interaction between abacavir (1592, ABC) and ethanol (ETOH) in HIV-infected subjects (S).* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst A-67.

46. Tisdale, M., Alnadaf, T., Cousens, D. *Combination of mutations in human immunodeficiency virus type 1 reverse transcriptase required for resistance to the carbocyclic nucleoside 1592U89.* Antimicrob Agents Chemother 1997, 41: 1094-8.

47. Harrigan, R., Stone, C., Griffin, P. et al. *Antiretroviral activity and resistance profile of the carbocyclic nucleoside HIV reverse transcriptase inhibitor 1592U89.* 4th Conf Retroviruses Opportunistic Infect (Jan 22-26, Washington DC) 1997, Abst.

48. Tisdale, M., Najera, I., Cousens, D. *Analysis of resistant variants isolated on passage with the carbocyclic nucleoside analogue 1592U89.* J Acq Immune Defic Syndr Hum Retrovirol 1995, 10(Suppl. 3): Abst 9.

49. Pauwels, R., Hertogs, K., Peeters, F., Lanier, R., Graham, N., Mellors, J., Stoffels, P. *Susceptibility profile (Antivirogram™) of 945 clinical HIV-1 isolates to abacavir.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 41226.

50. *FDA committee favors accelerated approval of Ziagen.* Daily Essentials Nov 3, 1998.

Additional References

Mellors, J.W., Hertogs, K., Peeters, F., Lanier, R., Miller, V., Graham, N., Larder, B., Stoffels, P., Pauwels, R. *Susceptibility of clinical HIV-1 isolates to 1592U89.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 687.

Roy, A.K., Varlashkin, P., Long, S. *Identification and characterization of GW 1592U89 succinate polymorphic forms.* Pharm Res 1996, 13(9, Suppl.): Abst PDD 7456.

Zimmerman, T.P., Mahony, W.B., Domin, B.A., Prus, K.L. *Membrane permeation characteristics of the structurally related anti-HIV agents 1592U89 and (–)-carbovir in human erythrocytes and human T-lymphoblastoid CD4⁺ CEM cells.* Antivir Res 1995, 26(3): Abst 109.

Mahony, W.B., Domin, B.A., Prus, K.L., Zimmerman, T.P. *Membrane permeation characteristics of the structurally related anti-HIV agents 1592U89 and (–)-carbovir in human erythrocytes and human T-lymphoblastoid CD4⁺ CEM cells.* Proc Amer Assoc Cancer Res 1995, 36: Abst 2211.

Bilello, J.A., Bilello, P.A., Symonds, W., McDowell, J., Sadler, B., Bye, A., Drusano, G.L. *1592U89, a novel carbocyclic nucleoside analog with potent anti-HIV activity, is synergistic in combination with 141W94 an HIV protease inhibitor.* 4th Conf Retroviruses Opportunistic Infect (Jan 22-26, Washington DC) 1997, Abst.

Bilello, J.A., Bilello, P.A., Symonds, W., McDowell, J., Drusano, G.L. *Physiological concentrations of human albumin or alpha1-acid glycoprotein do not markedly alter the anti-HIV activity of 1592U89, a novel inhibitor of the HIV-1 reverse transcriptase.* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst I8.

Bilello, J.A., Bilello, P.A., Symonds, W., Gregg, F., Drusano, G.L. *Amprenavir (141W94) in combination with 1592U89 is highly synergistic in vitro.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-21.

Faletto, M.B., Miller, W.H., Garvey, E.P., Reardon, J.E., Good, S.S. *Unique intracellular activation of a new anti-HIV agent (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (1592U89) in the human T-lymphoblastoid cell line CEM-T4.* 34th Intersci Conf Antimicrob Agents Chemother (Oct 4-7, Orlando) 1994, Abst I84.

Faletto, M.B., Miller, W.H., Garvey, E.P., St. Clair, M.H., Hazen, R.J., Daluge, S.M., Good, S.S. *Unique purine crossover activation pathway for the potent anti-HIV agent 1592U89.* Antivir Res 1995, 26(3): Abst 68.

Thompson, M., Enstrom, T., Bohn, H., Savla, J., Weinberg, W., Wang, L., Johnson, J. *Single-dose plasma profiles of abacavir (1592, ABC) in renal failure.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 42278.

Good, S.S., Daluge, S.M., Ching, S.V. et al. *1592U89 succinate – Preclinical toxicological and disposition studies and preliminary clinical pharmacokinetics.* Antivir Res 1995, 26(3): Abst 8.

Schooley, R.T. et al. *Preliminary data from a phase I/II study on the safety and antiviral efficacy of the combination of 141W94 plus 1592U89 in HIV-infected patients with 150 to 400 CD4+ cells/mm³.* 4th Conf Retroviruses Opportunistic Infect (Jan 22-26, Washington DC) 1997, Abst.

Miller, V., Stürmer, M., Staszewski, S. et al. *The M184V mutation in HIV-1 reverse transcriptase (RT) conferring lamivudine resistance does not result in broad cross-resistance to nucleoside analogue RT inhibitors.* AIDS 1998, 12: 705-12.

Lanier, E.R., Stone, C., Griffin, P. et al. *Phenotypic sensitivity to 1592 (abacavir) in the presence of multiple genotypic mutations: Correlation with viral load response.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 686.

Prins, J., Jurriaans, S., Roos, M., De Wolf, F., Miedema, F., Lange, J. *An attempt at maximally suppressive anti-HIV therapy.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 385.

Gilson, I., Busalacchi, M. *Abacavir/efavirenz/adefovir salvage regimen for refractory HIV disease.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-200.

McDowell, J.A., Symonds, W.T., LaFon, S.W. et al. *Single-dose and steady-state pharmacokinetics of escalating regimens of 1592U89 with and without zidovudine.* 11th Int Conf AIDS (July 7-12, Vancouver) 1996, Abst Mo.B.1140.

Kelleher, D., Mellors, J., Lederman, M., Haas, D., Cooney, E., Horton, J., Stanford, J., Haubrich, R. *Activity of abacavir (1592, ABC) combined with protease inhibitors (PI) in therapy naive patients.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12210.

Sonnerborg, A., Lancaster, D., Torres, R. *The safety and antiviral effect of 1592U89, alone and in combination with zidovudine in HIV-1 infected patients with CD4$^+$ counts 200-500 cells/mm^3.* AIDS 1996, 10(Suppl. 2): Abst OP4.1.

Staszewski, S., Katlama, C., Harrer, T., Massip, P., Yeni, P., Cutrell, A., Tortell, S.M., Steel, H.M., Lanier, E.R., Pearce, G. *Preliminary long-term open-label data from patients using abacavir (1592) containing, antiretroviral treatment regimens.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 658.

Drusano, G.L., Preston, S.L., Bilello, J.A. et al. *A new method for evaluation of combination chemotherapy regimens: Application to abacavir (1592U89 - ABC) and amprenavir (141W94 - APV).* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst A-5.

Foster, R.H., Faulds, D. *Abacavir*. Drugs 1998, 55: 729-36.