

Zidovudine, Lamivudine, and Abacavir

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ZIDOVUDINE

Introduction

The history of the discovery and development of zidovudine (ZDV; or 3'-azido-3'-deoxythymidine, AZT, or Retrovir[™], formerly BW A509U) is fascinating not only because it was the first Food and Drug Administration (FDA)-approved agent for the treatment of HIV, but for the unprecedented speed with which this drug moved through the new-drug approval process (Table 1). In March 1987, ZDV was approved by the FDA for use in HIV-infected individuals with a previous episode of *Pneumocystis carinii* pneumonia (PCP) and/or a CD4 cell count of less than 200 cells/mm³. The use of ZDV in asymptomatic or symptomatic patients with CD4 cell counts greater than 500 cells/mm³ was approved in March 1990. ZDV was initially approved as a monotherapy. Subsequently, ZDV was approved for use in combination regimens with zalcitabine and lamivudine (3TC, Epivir[®]). Although early studies demonstrated clinical and survival benefits of ZDV alone or in combination with other nucleoside analogs, these benefits were of limited durability because of incomplete virological suppression and the emergence of resistant HIV strains. ZDV is currently approved for the treatment of HIV infection in combination regimens with potent antiretroviral agents, including HIV protease inhibitors (PIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); and potent nucleoside reverse transcriptase inhibitors (NRTIs), such as abacavir (ABC).

Preclinical Development

ZDV was initially synthesized as a potential antineoplastic agent by Horwitz and colleagues in 1964 (1). However, it was never approved for use in humans as a cancer chemotherapy. In 1974, Ostertag et al. were the first to describe the antiretroviral activity of ZDV by demonstrating inhibition of the spleen focus-forming virus, a murine type C retrovirus (2). In 1985, Mitsuya and collaborators showed that ZDV was a potent inhibitor of the *in vitro*

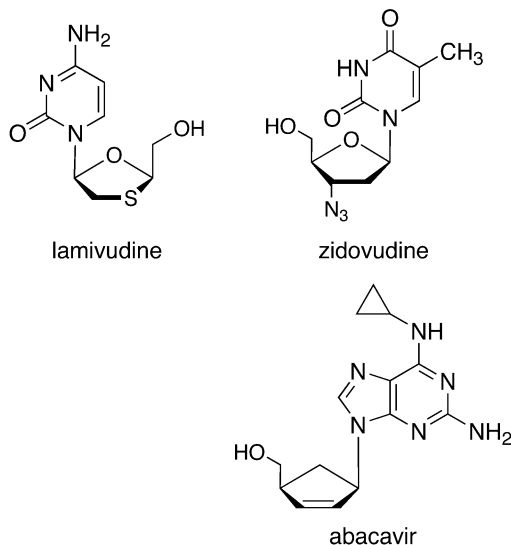


Fig. 1. Chemical structures of the drugs discussed in this chapter.

amprenavir, and lopinavir), and interferon- α (5–11). The combination of ZDV and stavudine (d4T) shows antagonistic activity *in vitro* against several isolates of HIV (12). Ribavirin antagonizes the antiviral activity of ZDV *in vitro* by inhibiting ZDV phosphorylation (13).

ZDV Pharmacokinetics

ZDV crosses the blood–brain barrier and has a cerebrospinal fluid (CSF)-to-plasma ratio of 0.25 (14). The compound is metabolized by the liver, primarily by glucuronidation, and then excreted by the kidneys (15). It is well-absorbed in the gut, with an average bioavailability of approx 60%, and is approx 35% protein bound. After oral dosing, the peak serum concentration is achieved in 0.5 to 1.5 h. Food decreases peak plasma concentrations by more than 59%. However, total exposure, as reflected by the area under the concentration curve (AUC), is unchanged. The mean serum half-life is 1.1 h and the intracellular half-life is 3 h. ZDV 5'-triphosphate, however, has an intracellular half-life of approx 3 to 4 h, and, in treated patients, it is stable for 6 h after dosing. ZDV is present in breast milk and crosses the placenta (16). ZDV is also detected in the semen, with a semen-to-serum ratio ranging from 1.3 to 20.0 (17). No dose adjustment is required for patients with severe renal dysfunction. Hemodialysis and peritoneal dialysis seem to have a negligible effect on the removal of ZDV (18). The pharmacokinetics of ZDV seem unchanged during pregnancy (19). ZDV concentrations in newborns are equivalent to maternal levels.

Phase I/II Studies

On June 14, 1985, the Burroughs-Wellcome Company submitted an application for an investigational new drug (IND) exemption for the use of ZDV in humans. Seven days later, the FDA approved the exemption, and, on July 3, 1985, the first patient was treated with ZDV. The phase I study was a 6-wk trial of four ZDV dose regimens involving 19 patients with AIDS or AIDS-related complex (ARC) and was conducted at the National Cancer Institute and Duke University Medical Center (20). ZDV was administered intravenously for 2 wk, then orally for 4 wk at twice the intravenous dose. ZDV was well-absorbed from the gut and crossed the blood-brain barrier. Therapeutic levels were maintained with either 5 mg/kg of ZDV administered intravenously or 10 mg/kg of ZDV administered orally, every 4 h. There were no treatment-limiting side effects. The most common side effects were headaches and depressed white blood cell counts, which were not dose related. Fifteen of the 19 patients had increases in their CD4 cell counts during therapy, 6 previously anergic patients showed restoration of delayed-type hypersensitivity skin test reactions, 2 patients had resolution of chronic fungal nailbed infections without specific anti-fungal therapy, and the entire cohort had an average weight gain of 2.2 kg.

ZDV Monotherapy

Advanced HIV Disease

In February 1986, a multicenter, double-blind, placebo-controlled trial of ZDV involving 282 patients was begun (Table 2) (21). Patients were enrolled who were within 4 mo of diagnosis of PCP or had ARC. Patients were randomized to receive either 250 mg ZDV or placebo, every 4 h for a total of 24 wk. By September 1986, 19 patients taking placebo but only 1 patient taking ZDV had died. The placebo arm of the trial was discontinued and all patients previously administered placebo were offered open-label ZDV. Other findings of the study included a decreased incidence of opportunistic infections, increased CD4 cell counts, and weight gain in the ZDV group.

At that time, it was recognized that a mechanism was needed to provide ZDV to seriously ill HIV-infected patients while awaiting clinical trial data analysis and regulatory review. A compassionate plea program (Treatment IND) was established to provide ZDV to patients with a previous episode of PCP. The Treatment IND was in place from October 11, 1986 through March 24, 1987, during which time, 4805 patients received ZDV therapy. In late March 1987, ZDV was approved for patients with a previous episode of PCP or whose CD4 cell count was below 200 cells/mm³.

Mildly Symptomatic HIV Disease

In a double-blind, placebo-controlled trial conducted by the newly formed AIDS Clinical Trials Group (ACTG) 016, 711 people with mildly symptomatic HIV disease were stratified by pretreatment CD4 cell counts of between 200 and 500 cells/mm³, or at least 500 but fewer than 799 cells/mm³ (22). Three hundred fifty-one subjects were assigned to placebo and 360 subjects were assigned to 200 mg ZDV every 4 h for a median duration of follow-up of 11 mo. Clinical endpoints were the development of AIDS, development of ARC, or death. In the subgroup of patients with CD4 cell counts between 200 and 500 cells/mm³, 34 endpoints occurred in the placebo group and 12 in the ZDV-treated group. The ZDV-treated group had significant increases in CD4 cell counts and weight gain. No benefit in time to progression to a clinical endpoint was found in the subgroup with CD4 cell counts greater than 500 cells/mm³; however, this group did have significant increases in the number of CD4 cells that persisted for 8 wk.

The Veteran Affairs Cooperative Study compared early vs late initiation of ZDV therapy in 338 patients with CD4 cell counts between 200 and 500 cells/mm³ (23). Early therapy consisted of 250 mg ZDV every 4 h, whereas late therapy was placebo until the CD4 cell count dropped below 200 cells/mm³ or until an AIDS-defining event occurred, at which time the same 1500 mg daily dose of ZDV was initiated. During a mean follow-up of more than 2 yr, there were 23 deaths in the early therapy group and 20 deaths in the late-therapy group. Twenty-eight patients in the early therapy group and 48 patients in the late-therapy group progressed to AIDS. There was an increased time to reach a CD4 cell count of fewer than 200 cells/mm³ and an increased incidence of side effects in the early treatment group.

Asymptomatic HIV Disease

The first large study of the efficacy of ZDV in asymptomatic HIV-infected patients was ACTG 019. This was a three-arm study to determine the safety and efficacy of ZDV at two different daily doses (100 mg or 300 mg every 4 h, 5 doses/d) compared with placebo in patients with CD4 cell counts either above or below 500 cells/mm³. Volberding et al. reported the initial results in asymptomatic patients with CD4 cell counts fewer than 500 cells/mm³, after a mean follow-up of 55 wk (24). Thirty-three of 428 patients in the placebo group progressed to AIDS, as compared with 11 of 453 patients in the 500 mg ZDV daily group and 14 of 457 patients in the 1500 mg ZDV daily group. The ZDV treatment groups had significant increases in their CD4 cell counts and significant declines in their HIV p24 antigen levels compared with placebo recipients. Higher-dose therapy recipients had more adverse effects than those in the lower-dose group. In August 1989, on the basis of evidence that treatment at

Table 2
Major Studies of Zidovudine Monotherapy^a

Trial (ref.)	Design	Dosage	No. of subjects	Entry criteria	Entry CD4 cell count (cells/mm ³)
BW 002 (21)	Placebo-controlled, randomized, double-blind	250 mg ZDV q4 h	282	AIDS or ARC; CD4 < 100 cells/mm ³ ; CD4 101–499 cells/mm ³	49 and 54 (median); 128 and 190 (median)
ACTG 016 (22)	Placebo-controlled, randomized, double-blind	200 mg ZDV q4 h	711	Mildly symptomatic; CD4 200–800 cells/mm ³	225 (median)
ACTG 019 (24)	Placebo-controlled, randomized, double-blind	300 mg or 100 mg ZDV 5 times daily	1338	Asymptomatic; CD4 < 500	350 (median)
VA Study (23)	Placebo-controlled, randomized, double-blind	250 mg ZDV q4 h Open label ZDV when CD4 < 200	338	Mildly symptomatic; CD4 200–500 cells/mm ³	355 (mean)
Concorde (26)	Placebo-controlled, randomized, double-blind	250 mg ZDV QD	1749	Asymptomatic	≤200, 6%; 201–500, 52%; >500, 42%
ACTG 019 (27)	Placebo-controlled, randomized, double-blind	300 mg or 100 mg ZDV 5 times daily; Open label after 1989 for CD4 < 500 cells/mm ³	1637	Asymptomatic CD4 > 500 cells/mm ³	655 (median)

Table 2 (*Continued*)

CD4 cell count response (cells/mm ³)	Antiviral response	Clinical outcome	Comments
Increased CD4 count in ZDV group	P24 antigenemia decreased in ZDV group	ZDV improved survival and decreased number of opportunistic infections in 24-wk period	
Increased +44 in patients with entry counts 200–500 cells/mm ³ ; no significant changes for those with entry counts >500 cells/mm ³	Serum p24 antigen levels decreased significantly for ZDV group	At CD4 200–500 cells/mm ³ , ZDV delays progression to AIDS but no delay with CD4 > 500 cells/mm ³ ; no survival benefit seen	Little toxicity in these mildly symptomatic subjects
Median change +39 in 500 mg ZDV; +26 in 1500 mg ZDV; and –16 in placebo group	Significant improvements in p24 antigenemia in both ZDV groups	Lower rate of progression to AIDS in ZDV groups; no survival benefit of ZDV	Higher dose ZDV had more severe hematological toxicity
At 20 mo, mean changes = –35.5 early therapy; –83.6 late therapy	Conversion to p24 antigen seronegative; 79% early therapy; 35% late therapy	ZDV slowed progression; no survival benefit	More side effects in early therapy group
Increase of 20 in immediate therapy group c/w decrease of 9 in deferred therapy group at 3 mo	Not reported	No significant benefit in progression or mortality with early ZDV	Time-limited benefit of ZDV monotherapy shown
Median interval to decline of CD4 to <500 significantly longer in immediate therapy group c/w deferred group	Not reported	No difference in duration of overall or AIDS-free survival between early and deferred-therapy groups	Toxicity greater with higher dose ZDV

^aq4 h, every 4 hours; QD, once daily; c/w, compared with

the lower dosage delayed the progression of disease in patients with initial CD4 cell counts below 500 cells/mm³, the placebo arm of the substudy was terminated and all subject were offered open-label ZDV at 500 mg/d. In a subsequent evaluation of the cohort with CD4 cell counts of fewer than 500 cells/mm³, after a mean follow-up of 2.6 yr, ZDV at 500 mg daily was still found to result in a significant delay in progression to AIDS or death, but there was no survival benefit associated with earlier use compared with delayed ZDV initiation (25).

The Concorde Study conducted by the European Collaborative Group was the second large-scale clinical trial to address the efficacy of early ZDV therapy for HIV infection (26). One thousand seven hundred forty-nine asymptomatic patients were randomized to either ZDV (immediate-treatment group) or placebo (delayed-treatment group) and followed for a mean of 3.3 yr. There was no significant benefit in the immediate-treatment group regarding mortality or progression to AIDS or ARC, with 29% of patients in the immediate-treatment group vs 32% of patients in the delayed-treatment group reaching one of these endpoints. However, there were differences in the CD4 cell counts between the two groups over time, with median CD4 cell count changes from baseline to 3 mo of +20 cells for the immediate-treatment group and -9 cells for the delayed-treatment group.

Finally, the second substudy of ACTG 019, in the cohort of patients with CD4 cell counts greater than 500 cells/mm³ was reported in 1995 (27). Volberding et al. described no difference in duration of overall or AIDS-free survival between early and deferred-treatment groups. The results of these ZDV monotherapy studies suggested that the efficacy of ZDV used alone in the treatment of patients with either mildly symptomatic or asymptomatic HIV infection was of time-limited benefit and provided minimal survival advantage.

ZDV for Prevention of Mother-to-Child Transmission

ZDV is approved for use in HIV-infected women and their infants for the prevention of perinatal transmission of HIV. In the landmark study, Pediatric AIDS Clinical Trials Group (PACTG) 076, ZDV was administered to pregnant women antepartum starting at 14 to 34 wk, intrapartum at 2 mg/kg during 1 h, then at 1 mg/kg/hr infusion; and administered to the newborn at 2 mg/kg orally, four times daily, for 6 wk. There was an 8.3% risk of HIV infection in the ZDV-treated group compared with a 25.5% risk in the placebo group, a 67.5% reduction in relative risk of HIV transmission (28). A detailed discussion of prevention of vertical transmission may be found in Chapter 15.

ZDV Nucleoside Combination Therapy

Several large studies have demonstrated that ZDV combined with other nucleoside agents provide improved and more durable clinical and survival

benefits compared with ZDV alone (Table 3). The Delta trial evaluated ZDV monotherapy vs combination therapies of ZDV plus zalcitabine or ZDV plus didanosine in both ZDV-naïve and ZDV-experienced patients (29). At a median follow-up of 30 mo, ZDV-naïve patients had a 42% relative reduction in mortality with the ZDV plus didanosine combination and a 32% relative reduction in mortality with the ZDV plus zalcitabine combination compared with ZDV monotherapy. In ZDV-experienced patients, the addition of didanosine improved survival, with a relative reduction in mortality of 23%, but there was no direct evidence of benefit with the addition of zalcitabine (relative reduction, 9%).

Similarly, ACTG 175 evaluated treatment with ZDV alone, didanosine alone, ZDV plus didanosine, or ZDV plus zalcitabine in ZDV-naïve and ZDV-experienced patients (30). The progression to a primary endpoint of either at least a 50% decline in CD4 cell count, development of AIDS, or death was more frequent with ZDV alone (32%) than with ZDV plus didanosine (18%), ZDV plus zalcitabine (20%), or didanosine alone (22%) in both ZDV-naïve and ZDV-experienced patients. For ZDV plus zalcitabine, the benefits were limited to patients without previous ZDV treatment. The combination of ZDV and 3TC has also proven to be a potent nucleoside combination (*see* “Lamivudine” section). In several large trials, benefits were demonstrated in CD4 and HIV RNA responses, disease-free survival, and overall survival.

ZDV in Triple-Combination Therapy

It soon became apparent that dual nucleoside analog combination therapy also had limited durability, attributed in part to the same factors that made ZDV monotherapy of limited use, incomplete suppression of viral replication and development of resistant virus. Focus turned toward development of agents with different mechanisms of action than the NRTIs. With the discovery and development of NNRTIs and PIs came knowledge that potent combination regimens, particularly three-drug regimens containing these new agents, provided greater virological and immunological benefits than were seen with nucleoside analogs alone.

The Italy, the Netherlands, Canada, and Australia Study (INCAS) compared the virological effects of ZDV plus nevirapine, ZDV plus didanosine, and ZDV plus didanosine plus nevirapine in antiretroviral-naïve patients (31). The triple-therapy group had the greatest virological effect. ACTG 229 evaluated ZDV in combination with the PI, SQV; ZDV plus SQV plus 2',3'-dideoxycytidine (ddC); and ZDV plus ddC in patients with 4 mo of previous ZDV use (32). Studies combining ZDV and 3TC with IDV, NFV, or EFV also showed improved virological and immunological benefits and are detailed in the “Lamivudine” section of this chapter. The results of these triple-combination studies provided data to support the use of ZDV and a second NRTI in combination with a third

Table 3
Clinical Trials of Zidovudine Combination Therapy^a

Trial (ref.)	Design	Dosage	No. of subjects	Entry criteria	CD4 cell count at entry (cells/mm ³)
Delta (29)	Randomized, double-blind; ZDV vs ZDV +ddC vs ZDV +ddl	ZDV 600 mg QD; ddI 400 mg QD; ddC 2.25 mg QD	3207 ZDV naive, <i>n</i> = 2124; Previous ZDV, <i>n</i> = 1083	AIDS and CD4 >50 cells/mm ³ ; no or minimal symptoms and CD4 <350 cells/mm ³ ; Delta 1: ZDV-naive; Delta 2: ZDV experienced	205 (mean)
ACTG 175 (30)	Randomized, double-blind; ddI vs ZDV vs ddI+ZDV vs ddC+ZDV	Same doses as Delta	2467 ZDV naive, <i>n</i> = 1060 Previous ZDV, <i>n</i> = 1407	No AIDS-defining illness; CD4 200–500 cells/mm ³ ; antiretroviral naive or experienced	352 (mean)
INCAS (31)	Randomized, double-blind placebo-controlled; ZDV+NVP vs ZDV+ddI vs ZDV+ddI+NVP	ZDV 200 mg TID; ddI 125 or 200 mg BID based on weight; NVP 200 mg QD for 2 wk, then 200 mg BID	Treatment naive <i>n</i> = 151	Antiretroviral naive; CD4 200–600 cells/mm ³	346–387 (mean)
ACTG 229 (32)	Randomized, double-blind placebo-controlled; SQV+HGC +ddC+ZDV vs SQV+HGC+ZDV vs ZDV+ddC	SQV 600 mg TID; ddC 0.75 mg TID; ZDV 200 mg TID	Previous ZDV <i>n</i> = 302	CD4 50–300 cells/mm ³	SQV+ddC +ZDV 145; SQV+ZDV 156; ddC +ZDV 171

Table 3 (Continued)

CD4 response	Antiviral response	Clinical outcome	Comments
Improved with both combinations c/w ZDV alone	Not stated	Decrease in mortality, 33% for ddI+ZDV and 21% for ddC+ZDV; Decrease in disease progression, 36% for ddI+ZDV and 17% for ddC+ZDV (for Delta 1 and 2 c/w ZDV alone)	For ZDV-naïve pts either combination had significant decrease in progression or death; for ZDV-experienced pts, no significant increase in CD4 count or clinical benefit with combination
Significant improvement in combination or ddI alone groups for both ZDV naïve and experienced	Not stated	Progression of AIDS-defining event or death or ≥50% decline in CD4 count: ZDV 32%, ZDV+ddI 18%, ZDV+ddC 20%, ddI alone 22%	Survival benefit for all combinations and ddI alone c/w ZDV monotherapy; ZDV+ddC benefits limited to ZDV-naïve pts
Triple therapy group with sustained increases at week 52	HIV RNA <20 for triple therapy 51%, ZDV+ddI 21%, ZDV+NVP 0% at wk 52	Rates of disease progression or death: ZDV+NVP 23%, ZDV+ddI 25%, triple therapy 12%	Triple drug therapy with greater and sustained decrease in HIV viral load
Significant improvements over baseline for triple therapy group at 24 wk	Mean HIV RNA decrease 0.4 log ₁₀ copies/mL for triple therapy; 0.1 log ₁₀ copies/mL for SQV +ZDV and ZDV+ddC groups over 24 wk	Not stated	Support for triple therapy to achieve CD4 cell count and viral load improvements

“QD, once daily; BID, twice daily; TID, three times daily; c/w, compared with; pts, patients

agent from either the NNRTI or PI class to create a potent and durable combination regimen.

ZDV in the Pediatric Population

ZDV was approved for use in HIV-infected children aged 3 mo to 12 yr in May 1990. It has good central nervous system penetration and is the NRTI of choice when treating children with HIV-related central nervous system disease. Pizzo et al. reported the results of continuous iv ZDV administration in 21 children (33). Thirteen children had neurodevelopmental abnormalities and 11 children had CD4 cell counts fewer than 200 cells/mm³. ZDV was administered at four dose levels: 0.5, 0.9, 1.4, and 1.8 mg/kg/h. Improvement in neurodevelopmental abnormalities occurred in all 13 children who had presented with encephalopathy before treatment. IQ scores increased in these 13 children and in 5 other children who had no detectable evidence of encephalopathy before treatment. Most patients also had increased appetite and weight, decreased lymphadenopathy and hepatosplenomegaly, and increased numbers of CD4 cells. Bone marrow suppression was the only evident toxicity, with dose-limiting neutropenia occurring in most patients who received doses of 1.4 mg/kg/h or more.

ZDV Monotherapy

Eighty-eight children with advanced HIV disease and a mean age of 3.9 yr received oral 180 mg/m² ZDV four times daily for 24 wk (34). After a median follow-up of 56 wk, one or more episodes of hematological toxicity occurred in 61% of children. Kaplan-Meier analysis demonstrated that the probability of survival was 0.89 after 24 wk and 0.79 after 52 wk. There was marked improvement in weight, cognitive function, and serum and CSF concentrations of HIV-1 p24 antigen. The authors concluded that this dose of ZDV can be safely administered to children with advanced HIV disease and that the immunological and virological improvements in children are similar to those seen in adults.

ZDV Combination Therapy

The PACTG Study 152 was a multicenter, double-blind study of 831 symptomatic HIV-infected children ages 3 mo through 18 yr. Ninety-two percent of children were antiretroviral-naïve (35). Patients were randomized to receive either 180 mg/m² ZDV four times daily, 120 mg/m² 2',3'-dideoxyinosine (ddI) twice daily, or ZDV plus ddI. The primary endpoint was length of time to death or to progression of HIV disease. An interim analysis at a median follow-up of 23 mo showed a significantly higher risk of HIV-disease progression or death in patients receiving ZDV alone than in those receiving combination therapy. The study arm with ZDV alone was stopped and unblinded. At the end of the study, ddI alone had an efficacy similar to ZDV plus ddI. The authors concluded that

in symptomatic children with HIV, treatment with either ddI alone or ZDV and ddI was more effective than treatment with ZDV alone.

ZDV Resistance

HIV resistance to ZDV is associated with the accumulation of specific mutations sites on the HIV *pol* gene that encode for the reverse transcriptase. The mutations associated with decreased ZDV susceptibility occur at amino acid sites 41, 67, 70, 215, and 219; sites 41, 70, and 215 are the most important sites of mutation (36,37). Cross-resistance to multiple nucleoside analogs, including ZDV, didanosine, zalcitabine, and d4T, has been demonstrated with mutations at sites 62, 75, 77, 116, and, most notably, 151. The presence of the M184V mutation, induced by 3TC and ABC, has been shown to induce ZDV hypersusceptibility of the virus and a resensitization of ZDV-resistant virus to ZDV (38,39).

Drug Interactions

Coadministration of ZDV with phenytoin may result in decreased levels of phenytoin. However, a pharmacokinetic study of a single 300-mg dose of phenytoin during steady-state ZDV administration showed no change in phenytoin kinetics (40). ZDV administration seems to have a negligible effect on methadone kinetics (41). Probenicid may increase ZDV levels through inhibition of glucuronidation and reduced renal excretion of ZDV (42). Rifampin coadministration resulted in an increase in ZDV clearance and a decrease in AUC; however, an increase in AUC and peak plasma concentrations were seen for the active metabolite, zidovudine triphosphate (ZDV-TP). Fluconazole dosed with ZDV showed a 74% increase in the AUC of ZDV and a 128% increase in its half-life. Atovaquone coadministration resulted in a 24% decrease in ZDV oral clearance and a 35% increase in AUC.

Current Clinical Use

ZDV Dosing and Formulations

The recommended daily dose of ZDV in adults is 600 mg daily, in two or three divided doses. This recommendation is based on studies of early and advanced HIV disease, which compared the initial 1200 mg/d dose with 100 mg five or six times daily and demonstrated equivalent efficacy and less hematological toxicity (43). In addition, in one study, ZDV administered for 48 wk at 100 mg every 4 h or at 300 mg every 12 h showed no significant difference in adverse events (44). ZDV dosing for pediatric patients 3 mo to 12 yr of age is 180 mg/m² every 6 h, not to exceed 200 mg every 6 h. ZDV is available in four formulations: a 300 mg tablet, a 100 mg capsule, a 50 mg/5 mL syrup, and a 10 mg/mL infusate.

Toxicity

Toxicities associated with ZDV include headache, myalgias, malaise, fatigue, nausea, anorexia, anemia, and neutropenia (45). Constitutional symptoms occurring with initiation of therapy can generally be managed symptomatically. Anemia and neutropenia are more common in patients with advanced HIV disease and, if severe, may necessitate discontinuation of ZDV, with substitution with a different antiretroviral agent. Use of other agents for treatment or prophylaxis of HIV-associated infections, such as trimethoprim/sulfamethoxazole and ganciclovir, may exacerbate the hematological perturbations. Long-term use of ZDV may be associated with muscle toxicity, hepatic toxicity, and nail hyperpigmentation.

Current Uses

Current clinical indications for the use of ZDV include HIV infection in which treatment is indicated, prevention of maternal–fetal transmission, and occupational postexposure prophylaxis. ZDV is currently recommended as part of an initial treatment regimen that includes a second NRTI plus an NNRTI or one or two PIs. The use of ZDV combined with a second NRTI and ABC as an initial therapy is recommended only in patients who cannot take a NNRTI or PI.

LAMIVUDINE

Introduction

3TC is the negative or *cis* enantiomer of 2'-dideoxy-3'-thiacytidine and has activity against HIV-1, HIV-2, and hepatitis B. This agent is a pyrimidine nucleoside analog in which the 3' carbon of the ribose ring of 2'-deoxycytidine has been replaced by a sulfur atom (Fig. 1). The drug was approved for use in adults in February 1995 and for children at least 3 mo of age in November 1996. 3TC is indicated for treatment of HIV infection only in combination with other antiretroviral agents.

Mechanism of Action and In Vitro Studies

3TC requires intracellular phosphorylation to become active and is preferentially active in resting cells. The active compound, 3TC-triphosphate, is a reverse transcriptase inhibitor that competes with deoxycytidine triphosphate, an endogenous nucleotide, for binding in the HIV reverse transcriptase-binding site. Insertion of 3TC-triphosphate into the proviral DNA leads to chain termination because 3TC lacks the 3' hydroxyl group necessary for the 5' to 3' linkage required for DNA synthesis (47). The compound was initially synthesized as a racemic mixture (BCH-189), and this mixture has potent activity in vitro against HIV-1, with a mean 50% inhibitory dose (IC_{50}) of $0.73 \mu M$ in an MT4 cell line assay (46). BCH-189 was also shown to have activity against

ZDV-resistant isolates and caused less cytotoxicity than ZDV (48). Subsequent analysis revealed that both the positive and negative enantiomers of BCH-189 had in vitro activity against HIV (49,50). The negative enantiomer (3TC) demonstrated greater anti-HIV activity, which is attributed to the compound's relative resistance to deoxycytidine deaminase, thus, preventing cleavage of the compound from the HIV RNA/DNA complex. In addition, the negative enantiomer has less in vitro bone marrow toxicity, relatively little activity against mammalian DNA polymerase- γ and, thus, little host mitochondrial toxicity in vitro (51,52). 3TC is highly active against HIV-1 in lymphoid cell assays and peripheral mononuclear cell lines, with an IC_{50} from 4 to 670 nM and 2.5 to 90 nM, respectively (51). 3TC has been shown to be synergistic or additive in vitro with NRTIs (ZDV, d4T, and didanosine), NNRTIs (nevirapine and delavirdine), and PIs (SQV and IDV) (53,54). 3TC interferes with the phosphorylation of zalcitabine, and the combination of these two agents may be antagonistic against HIV replication (55).

3TC Pharmacokinetics

3TC is rapidly absorbed after oral administration, with an absolute bioavailability of approx 86% in adults and 66% in children. Food has no significant effect on absorption. After oral administration of 2 mg/kg twice daily to nine adults with HIV, the peak serum 3TC concentration was 1.5 ± 0.5 (mean \pm SD) and well above the in vitro IC_{90} of HIV-1 (56). The CSF-to-plasma ratio of 3TC is 0.11. The serum half-life of 3TC is 2 h and its intracellular half-life is 10 to 15 h, allowing for twice-daily or once-daily dosing. Binding of 3TC to human plasma proteins is low, and 3TC freely crosses the placenta and crosses into breast milk (57). 3TC shows marked concentration in the male genital tract and the semen-to-blood concentration ratios for 3TC are higher than for other NRTIs, NNRTIs, or single PIs (58). The majority of the drug is eliminated unchanged in the urine (59). Dose adjustment is required if there is significant renal impairment. 3TC is cleared by hemodialysis but no dose adjustments are necessary because of its large volume of distribution (60).

Clinical Development-Phase I/II Studies

Early studies of 3TC as monotherapy were primarily small trials designed to study the drug's safety and pharmacokinetic parameters. In a multicenter, open-label, dose-escalating study, 97 patients with AIDS or ARC, and a CD4 cell count of fewer than 300 cells/mm³ were administered doses of 3TC ranging from 0.5 to 20 mg/kg/d for 24 wk (56). At the higher doses of 8 mg/kg/d and 12 mg/kg/d, transient decreases in p24 antigen and increases in CD4 cell counts were seen, but the CD4 counts subsequently decreased to baseline after 20 wk. Neutropenia was observed only at the 20 mg/kg/d dose. In a second dose-esc-

lating study, 104 asymptomatic or mildly symptomatic HIV-infected patients with CD4 cell counts of at most 400 cells/mm³ were also administered doses of 3TC ranging from 0.5 to 20 mg/kg/d (61). Sustained decreases in p24 antigenemia independent of dose were seen over the 52-wk study. Small and transient increases in CD4 cell counts were detected during the first 4 wk of treatment. No dose-limiting toxicities were observed. Schuurman et al. demonstrated an initial decline in HIV-1 p24 antigenemia and RNA viral load in the first 2 wk of 3TC monotherapy, followed by a rise in both values that coincided with the appearance of 3TC-resistant viruses in plasma (62). This study was one of the initial trials that demonstrated emergence of resistant virus with 3TC monotherapy.

Double-Combination Therapy

Protocol NUCA 3001 was a North American, randomized, double-blind trial comparing the safety and efficacy of 200 mg ZDV three times daily, 300 mg 3TC twice daily, 150 mg 3TC twice daily plus ZDV (low-dose combination), and 300 mg 3TC twice daily plus ZDV (high-dose combination) (Table 4) (63). Three hundred sixty-six patients were enrolled, of which 87% were men and 61% were white, with a median age of 34 yr. Eligible patients had received ZDV for 4 wk or less and had CD4 cell counts of 200 to 500 cells/mm³. The median CD4 cell count was 352 cells/mm³ and the mean baseline plasma HIV RNA level was 4.47 log₁₀ copies/mL. At 24 wk, the median change in log₁₀ HIV RNA was -0.31, -0.60, -1.20, and -1.10 for the ZDV only, 3TC only, low-dose combination therapy, and high-dose combination therapy groups, respectively. There was no difference in CD4 cell count or viral load changes within monotherapy or combination therapy groups. Protocol NUCB 3001 was a randomized, double-blind trial in Europe comparing ZDV monotherapy at 200 mg three times daily and 300 mg 3TC twice daily plus ZDV in 129 anti-retroviral-naïve adult patients with CD4 cell counts of 100 to 400 cells/mm³ (64). Seventy-four percent of the patients were men, 82% were white, the median age was 33 yr, and the median baseline CD4 cell count was 260 cells/mm³. CD4 cell count changes at 24 wk were -9 cells/mm³ for ZDV monotherapy and +78 cells/mm³ for the ZDV plus 3TC combination. Viral load decreases at 24 wk were -0.3 log₁₀ copies/mL for the ZDV group and -1.2 log₁₀ copies/mL for the ZDV plus 3TC group.

In protocol NUCA 3002, conducted in North America, 254 patients with previous ZDV monotherapy for at least 24 wk (83% men, 63% white; median age, 37 yr) were randomized to one of three treatment arms: 300 mg 3TC twice daily plus 200 mg ZDV three times daily, 150 mg 3TC twice daily plus 200 mg ZDV three times daily, or 200 mg ZDV three times daily plus 0.75 mg ddC three times daily (65). The use of ZDV was open label, whereas ddC and 3TC were double blind. Eligible patients had CD4 cell counts between 100 and 300

cells/mm³ and had been on ZDV monotherapy at least 24 wk. The baseline median CD4 cell count was 211 cells/mm³ and the mean baseline plasma HIV RNA was 4.60 log₁₀ copies/mL. At 24 wk, the CD4 cell count change was -16 cells/mm³ for the ZDV plus ddC group, and +31 cells/mm³ and +15 cells/mm³ for the low- and high-dose 3TC plus ZDV combination groups, respectively. Significant decreases in HIV RNA were found in the ZDV plus 3TC groups compared with the ZDV plus ddC group. There was no clear benefit of the higher 3TC dose. Protocol NUCB 3002 was a randomized, controlled trial performed in Europe, comparing ZDV monotherapy and 3TC plus ZDV in patients with CD4 cell counts between 100 and 400 cells/mm³ and at least 24 wk of ZDV (66). Two hundred twenty-three patients (83% men; 96% white; median age, 36 yr) were randomized to receive one of three regimens: 200 mg ZDV three times daily, 200 mg ZDV three times daily plus 150 mg 3TC twice daily, or 200 mg ZDV three times daily plus 300 mg 3TC twice daily. The absolute change in CD4 cell counts at 24 wk favored either combination therapy, with no difference noted between the two 3TC dose-containing regimens. Median reduction of HIV RNA at 24 wk was -0.9 log₁₀ copies/mL and -0.7 log₁₀ copies/mL for low- and high-dose 3TC plus ZDV combinations, respectively, whereas patients receiving ZDV monotherapy had an increase in HIV RNA of 0.2 log₁₀ copies/mL.

3TC in Triple-Combination Therapy

Multiple trials have investigated the combination of 3TC with ZDV or d4T and a PI or an NNRTI and demonstrated the potency of these combinations (Table 4). AVANTI 2 was a trial of antiretroviral-naïve patients to evaluate the efficacy of ZDV plus 3TC combination therapy compared with ZDV plus 3TC plus IDV (67). At week 52, the proportions of patients with a plasma HIV-1 RNA level less than 500 copies/mL were 75% and 23% in the triple- and double-therapy groups, respectively. The median CD4 cell count increase at week 52 was 177 cells/mm³ in the triple-therapy group and 91 cells/mm³ in the ZDV plus 3TC group. Similarly, ACTG 320 evaluated the combination of ZDV plus 3TC vs ZDV plus 3TC plus IDV in patients with at least 3 mo of previous ZDV therapy (68). Clinical endpoints were progression of disease, survival, CD4 cell count change, and plasma HIV-1 RNA change. Patients were followed for a median of 38 wk. Six percent of patients in the triple-therapy group had AIDS-defining events or died, compared with 11% in the double-therapy group. At week 24, the proportions of patients with plasma HIV-1 RNA levels less than 400 copies/mL were 60% and 9% for the triple- and double-therapy groups, respectively. The mean CD4 cell count increases were 121 cells/mm³ in the triple-therapy group compared with 40 cells/mm³ in the double-therapy group.

Table 4
Clinical Trials of 3TC Combination Therapy

Trial (ref.)	Design	Dosage	No. of subjects	Entry criteria	Entry CD4 cell Trial counts (cells/mm ³)
NUCA 3001 (63)	Randomized, double-blind; 3TC vs ZDV vs ZDV+3TC (low dose) vs ZDV + 3TC (high dose)	ZDV 200 mg TID; 3TC 150 mg BID (low dose); 300 mg BID (alone and high dose)	366	ZDV <4 wk; CD4 200–500 cells/mm ³	352
NUCB 3001 (64)	Randomized, double-blind; ZDV vs 3TC+ZDV	ZDV 200 mg TID; 3TC 300 mg BID	129	ZDV <4 wk; CD4 100–400 cells/mm ³	ZDV, 250; ZDV +3TC, 260 (median)
NUCA 3002 (65)	Randomized, double-blind; ZDV+ddC vs ZDV+3TC (2 doses)	ZDV 200 mg TID; 3TC 150 mg BID or 300 mg BID; ddC 0.75 mg TID	254	ZDV >24 wk; CD4 100–300 cells/mm ³	211 (median)
NUCB 3002 (66)	Randomized, double-blind ZDV vs ZDV 3TC (low dose or high dose)	ZDV 200 mg TID; 3TC 150 mg BID or 300 mg BID	223	ZDV >24 wk; CD4 100–400 cells/mm ³	ZDV, 250; ZDV+3TC low dose, 250; ZDV+3TC high dose, 230 (medians)

AVANTI 2 (67)	Randomized, double-blind, ZDV +3TC vs ZDV+3TC+IDV	ZDV 200 mg TID; 3TC 150 mg BID; IDV 800 mg TID	103	Treatment naïve	2-Drug group, 270; 3-drug group, 280 (median)
ACTG 320 (68)	Randomized, double-blind; ZDV +3TC vs ZDV+3TC+IDV	ZDV 200 mg TID, 3TC 150 mg BID, IDV 800 mg TID	1156	ZDV ≥ 3 mo	87
AVANTI 3 (69)	Randomized, double-blind; ZDV +3TC vs ZDV+3TC+NFV	ZDV 200 mg TID; 3TC 150 mg BID; NFV 750 mg TID	102	Treatment naïve	2-Drug group, 279; 3-drug group, 287 (median)
Murphy, et al. (70)	Randomized, comparison of doses of lopinavir (LPV) and ritonavir (RTV) with d4T and 3TC added at 3 wk (group 1) or at day 0 (group 2)	LPV plus RTV (400 mg/100 mg or 200 mg/100 mg); ZDV 300 mg BID; d4T 40 mg BID	100	Treatment naïve	Group 1, 398 Group 2, 310 (median)
Staszewski, et al. (71)	Open label; ZDV+3TC+EFV; ZDV+3TC+IDV; EFV+IDV (low dose)	ZDV 300 mg BID; 3TC 150 mg BID; EFV 600 mg QD; IDV 800 mg TID or 100 mg TID	450	No previous 3TC, NNRTI, or PI	345 (median)

(Continued)

Table 4 (Continued)

Duration of follow-up	CD4 response (cells/mm ³)	Antiviral response	Comment
24 wk (28-wk extension phase)	ZDV, +17; 3TC, +24; low-dose 3TC+ZDV, +55; high-dose 3TC+ZDV, +45	ZDV, -0.31 log ₁₀ copies/mL; 3TC, -0.60 log ₁₀ copies/mL; Low dose 3TC, -1.20 log ₁₀ copies/mL; high dose 3TC, -1.10 log ₁₀ copies/mL	No difference in CD4 cell count or viral load changes within monotherapy or combination therapy groups
24 wk (24-wk extension phase)	ZDV -9; ZDV+3TC, +78	ZDV, -0.3 log ₁₀ copies/mL; ZDV +3TC, -1.2 log ₁₀ copies/mL	Combination ZDV plus 3TC with larger CD4 and viral load changes than ZDV alone
24 wk	ZDV+ddC -16; ZDV+3TC (low dose) +31; ZDV+3TC (high dose) +15	Significant decreases for ZDV+3TC vs ZDV+ddC	No clear benefit of higher dose 3TC
24 wk	ZDV, -28; 3TC (low dose), +40; 3TC (high dose), +35	ZDV, +0.7 log ₁₀ copies/mL; 3TC, -0.9-0.65 log ₁₀ copies/mL	Combination ZDV +3TC with larger CD4 and viral load changes than ZDV alone

52 wk	Dual therapy, +91; triple therapy, +177	Proportion with HIV-RNA <500: 75% for triple therapy vs 23% for dual therapy	Triple combination with larger VL and CD4 changes than dual therapy but VL \leq 20 seen in only 46% of patients with IDV
38 wk (median)	Dual therapy, +40; triple therapy, +121 (24 wk)	Proportion with HIV-RNA < 400: 60% for triple therapy vs 9% for dual therapy (24 wk)	6% in triple therapy vs 11% in dual therapy developed AIDS defining event or died
52 wk	At week 28, triple therapy, +101.5; dual therapy, +47	Proportion with HIV-RNA <500: 83% for triple therapy vs 18% for dual therapy	Demonstrated virological superiority of combination ART regimens including PI's
48 wk	Group I +244; Group II +213 (mean)	75–79% with HIV RNA <50 copies/mL	Lpt plus rtv mean trough plasma concentrations 50–100 fold higher than protein-binding corrected EC50 for wild type HIV-1
48 wk	Range increase, 180–200	HIV RNA <400: ZDV+3TC+EFV, 70%; ZDV+3TC+IDV, 48%; EFV+IDV, 53%	More treatment discontinuation in IDV groups

^aQD, once daily; BID, twice daily; TID, three times daily

AVANTI 3 evaluated the use of ZDV plus 3TC and ZDV plus 3TC plus NFV in antiretroviral-naïve patients (69). At week 28, the proportions of patients with HIV-1 RNA levels less than 500 copies/mL were 83% and 18% for the triple- and double-therapy groups, respectively. Murphy et al. reported the results of a randomized, double-blind, multicenter trial of the combination of 3TC plus d4T plus the PI lopinavir (also known as ABT-378) combined with low-dose RTV in antiretroviral-naïve patients (70). Patients either began lopinavir/RTV alone with addition of 3TC plus d4T at week 3 (group 1) or received all agents together at day 0 (group 2). In an intent-to-treat analysis at 48 wk, HIV-1 RNA was less than 400 copies/mL for 91% (<50 copies/mL, 75%) and 82% (<50 copies/mL, 79%) of patients in groups 1 and 2, respectively. Staszewski et al. investigated the combination of 3TC paired with ZDV and combined with the NNRTI, EFV. In this study, the EFV group demonstrated greater virological suppression compared with an IDV-based regimen (71). At 48 wk, a significantly larger proportion of patients treated with 3TC plus ZDV plus EFV had HIV-1 RNA levels below 400 copies/mL than those treated with 3TC plus ZDV plus IDV or with IDV plus EFV (70% vs 48% vs 53%, respectively).

Pediatric Trials—3TC Monotherapy

In a phase I/II study, 90 children ages 3 mo to 17 yr were stratified into two arms based on previous antiretroviral use. Subjects received dosages of 3TC ranging from 1 to 20 mg/kg daily (72). CD4 and CD8 cell counts remained stable during 24 wk in therapy-naïve children and decreased slightly in previously treated children. Viral burden decreased by 0.43 log₁₀ copies/mL in both groups combined and by 0.68 log₁₀ copies/mL in the naïve group after 24 wk. Grouping patients into subsets of the lower (1 and 2 mg/kg/d), middle (4 and 8 mg/kg/d), and higher (12 and 20 mg/kg/d) dosage levels revealed significantly lower HIV RNA in children receiving at least 4 mg/kg/d 3TC. In vitro resistance to 3TC (M184V) was documented in sequential virus isolates from 20 of 26 patients after 8 to 48 wk of therapy. Increases in hepatic transaminases and development of pancreatitis were the most serious side effects.

Pediatric Combination Therapy—3TC and ZDV vs Didanosine

PACTG 300 was a multicenter, randomized, double-blind study that compared 4 mg/kg 3TC twice daily plus 160 mg/m² ZDV three times daily with 120 mg/m² didanosine monotherapy twice daily or a combination of ZDV plus 90 mg/m² ddI twice daily (73). A total of 471 symptomatic, antiretroviral therapy-naïve pediatric patients were enrolled. The median age was 2.7 yr, 58% were girls, and 86% were nonwhite. The mean baseline CD4 cell count was 868 cells/mm³ and the mean baseline plasma HIV RNA was 5.0 log₁₀ copies/mL. The median duration of follow-up was 10.1 mo for the ZDV plus

3TC arm and 9.2 mo for the ddI arm. Primary clinical endpoints were disease progression, including physical growth failure, central nervous system deterioration and Centers for Disease Control Clinical Category C, and death. In the 3TC plus ZDV arm, 6.4% of patients reached a clinical endpoint, as did 15.7% patients in the ddI arm. Both ZDV plus 3TC and ZDV plus ddI recipients had a lower risk of HIV disease progression than patients who received ddI alone ($p = 0.0026$ and $p = 0.0045$, respectively).

Pediatric Double Combination Therapy—Addition of 3TC to Current NRTI

The Pediatric European Network for Treatment of AIDS (PENTA)-4 study was a double-blind randomized trial of the addition of 3TC (4 mg/kg twice daily) or placebo to stable NRTI therapy in 162 pediatric patients with a median age of 6.5 yr, a median CD4 cell count of 328 cells/mm³, and a median HIV viral load of 4.9 log₁₀ copies/mL (74). Background therapy included ZDV in 52 patients, ddI in 39 patients, ZDV and ddI in 54 patients, and ZDV and ddC in 17 patients. At week 24, the addition of 3TC resulted in a median change in CD4 cell count of +47 cells/mm³ and an HIV viral load change of -0.3 log₁₀ copies/mL compared with placebo. The decrease in viral load was 0.38 log₁₀ copies/mL greater in the ZDV vs the ddI background therapy groups.

Pediatric Combination Therapy—3TC, ZDV, and RTV

As demonstrated in adults, the combination of 3TC with a second nucleoside analog and a PI seems to have an enhanced antiviral effect. In PACTG 338, an interim analysis demonstrated that children receiving RTV and one or two NRTIs had a mean decrease of greater than 1.5 log₁₀ copies/mL in viral RNA levels after 12 wk of therapy (75). After 48 wk, 42% of children receiving the triple combination of ZDV plus 3TC plus RTV had an undetectable viral load, as compared with 27% receiving a single NRTI plus RTV.

3TC Resistance

3TC monotherapy results in high-level HIV resistance, which is caused by a single mutation in codon 184 of the HIV-1 reverse transcriptase gene, in which methionine is replaced by either isoleucine or valine. In vitro experiments with 3TC demonstrated the IC₅₀ of these variants to 3TC is 500- to 1000-fold greater than that of wild-type virus (76). In vivo studies demonstrated an initial decline in HIV-1 p24 antigenemia and RNA viral load in the first 2 wk of 3TC therapy, followed by a rise in both values that coincided with the appearance of 3TC-resistant viruses in plasma (77). ZDV-resistant HIV isolates that acquire the M184V mutation have been found to regain their antiretroviral activity (78). The M184V mutation reverses the selective advantage ZDV-resistant strains

attain in continuation of HIV DNA chain elongation and, thus, leads to increased ZDV phenotypic susceptibility in the setting of genotypic resistance (79,80). In addition, HIV with the M184V mutation induced by either 3TC or ABC treatment results in increased tenofovir susceptibility for HIV in the presence or absence of ZDV-associated reverse transcriptase mutations. Other important mutations that confer 3TC resistance include groups of mutations based at codons 69 or 151.

Drug Interactions

Very few drug interactions between 3TC and other antiretroviral agents or other medications exist. 3TC coadministration with trimethoprim/sulfamethoxazole resulted in a 43% increase in AUC and a 35% decrease in renal clearance of 3TC (81). No changes in the pharmacokinetics of trimethoprim/sulfamethoxazole were seen.

Current Clinical Uses

Dosing and Formulations

The recommended daily dose of 3TC for adults is oral administration of either 150 mg twice daily or 300 mg daily, and for pediatric patients, 3 mo to 16 yr of age, is 4 mg/kg daily (up to a maximum daily dose of 300 mg). Dosage adjustment is recommended for creatinine clearance less than 50 mL/min. The drug is supplied in 150 mg and 300 mg tablets and as an oral solution of 10 mg/mL.

3TC dosed as a 300 mg tablet once daily was approved for use in June 2002. In a nonblind, sequential, pharmacokinetic study, 13 patients with HIV-1 infection received 150 mg 3TC twice daily and then switched to 300 mg once daily in randomized order (82). The plasma pharmacokinetic profile of 3TC was determined over a 12-h period on day 7 after twice-daily dosing and over 24 h on day 7 after once-daily dosing. Statistical analysis did not show a significant difference regarding the mean values of half-life, average steady-state concentration, or AUC between the two dosing regimens.

COLA4005 was a prospective, randomized, multicenter trial comparing the efficacy and safety of a switch to 3TC once-daily dosing vs continued standard dosing of 150 mg 3TC twice daily in subjects on a stable regimen with an HIV RNA level less than 400 copies/mL and CD4 cell counts greater than 50 cells/mm³ (83). At week 24, 82% of subjects on the once-daily regimen had HIV viral loads less than 50 copies/mL vs 81% on the twice-daily regimen. Both dosing regimens were well-tolerated with comparable safety profiles.

3TC is also available combined with ZDV alone and with ZDV plus ABC in a fixed-dose combination (FDC) tablet. The first coformulation of antiretroviral therapy, Combivir™ (COM) tablets contain 150 mg of 3TC and 300 mg of ZDV. COM was approved by the FDA in September 1997 for use in

HIV-infected adults and children greater than 12 yr of age. This drug is indicated for treatment of HIV infection in combination with other antiretroviral agents. Pharmacokinetic studies in adults revealed COM to be bioequivalent to one 150-mg 3TC tablet and one 300-mg ZDV tablet after single-dose administration to fasting healthy subjects (84). A randomized, open-label study in antiretroviral-experienced patients was performed to establish the clinical equivalence of COM plus a marketed PI, compared with a conventional regimen of 150 mg 3TC twice daily plus 300 mg ZDV twice daily plus a PI (85). In the 223 patients that were followed for 16 wk, the two regimens were shown to have equal efficacy. The FDC, 3TC plus ZDV plus ABC, known as Trizivir, is also available for treatment of HIV infection. A detailed discussion of Trizivir is presented in the “Abacavir” section of this chapter.

Toxicity

Significant toxicity related to 3TC is uncommon. The most common adverse effects described are headache, nausea, and neutropenia. The relative lack of neutropenia associated with 3TC use as compared with ZDV is likely related to decreased affinity of 3TC to human DNA polymerase. Pancreatitis has been reported in pediatric patients receiving 3TC, however, advanced HIV disease and concomitant medications may have contributed to these episodes (86). In adult clinical trials of 3TC, increased incidence of pancreatitis has not been demonstrated.

Current Use

Current indications for 3TC include HIV infection in which treatment is indicated, prevention of vertical transmission of HIV, occupational postexposure prophylaxis for HIV, and treatment of chronic Hepatitis B. 3TC is currently recommended as the nucleoside analog of choice combined with a second nucleoside analog (ZDV or d4T) or the nucleotide analog, tenofovir, to form the backbone of combination antiretroviral therapy in antiretroviral-naïve patients (87).

ABACAVIR

ABC (also known as Ziagen™, formerly 1592U89) is a synthetic carbocyclic nucleoside analog with potent and selective inhibitory activity against HIV-1. This agent was approved by the FDA for use in combination therapy of HIV-1 infection in adults and children age 3 mo or older in December 1998. ABC is currently recommended as an alternative agent to PIs or EFV in combination with two other NRTIs for initial treatment of established HIV infection (87).

Mechanism of Action and In Vitro Studies

Vince et al. reported the antiretroviral effects of the carbocyclic analog of 2',3'-dehydro-2',3'-dideoxyguanosine, a compound known as carbovir (Fig. 1)

(88). Initial data were based on analysis of the racemic mixture. Subsequent investigation revealed the negative enantiomer to be the biologically active isomer, and this compound became known as 1592U89 (89). ABC is anabolized intracellularly to its active triphosphate form via a unique metabolic pathway using enzymes that do not phosphorylate other NRTIs (90). Carbovir triphosphate is an analog of deoxy-guanosine-5'-triphosphate and inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate, deoxy-guanosine-5'-triphosphate, and by incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analog prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

The *in vitro* anti-HIV activity of ABC was demonstrated in a HIV-1 IIIB strain cultured in MT-4 cells, peripheral blood mononuclear cells, and macrophages, with IC_{50} values ranging from 4.0 to 0.65 μM (89). Eight clinical isolates of HIV-1 from ZDV-naïve patients amplified in peripheral blood mononuclear cells showed a mean IC_{50} of 0.26 μM (89,91). ABC demonstrated synergistic activity *in vitro* against HIV-1 when used in combination with ZDV, 3TC, didanosine, nevirapine, or amprenavir in MT4 cells (92–94). Additive effects with the other nucleoside analogs, such as d4T, were also noted.

Pharmacokinetics

ABC crosses the blood-brain barrier, with CSF-to-plasma concentration ratios of 18 to 25%. Bioavailability is 83% and serum half-life is 1.5 h. After oral administration of 300 mg ABC twice daily in 20 patients, the steady-state peak serum ABC concentration was $3.0 \pm 0.89 \mu g/mL$ (95). Binding of ABC to human plasma proteins is approx 50%, however, physiological concentrations of albumin or α -1-glycoprotein do not markedly alter ABC activity (96). Food intake does not affect the bioavailability of ABC. In humans, cytochrome P450 enzymes do not significantly metabolize ABC and it, in turn, does not inhibit human CYP3A4, CYP2C, or CYP2D6 activity at clinically relevant concentrations. The primary routes of elimination are metabolism by alcohol dehydrogenase and glucuronyl transferase. The pharmacokinetic properties of ABC have not been determined in patients with impaired renal function. In the CNAB1006 study, patients with mild liver impairment had a 1.9-fold increase in AUC and a 1.6-fold increase in ABC half-life, suggesting that patients with mild hepatic failure may need lower ABC doses to achieve similar AUCs to patients without liver disease (97).

Phase I/II Studies

Wang et al. reported results of 15 HIV-1 infected adults with a median CD4 cell count of 347 cells/mm³ who were enrolled in a randomized, seven-period crossover study (98). The pharmacokinetics and safety of single doses of ABC,

ZDV, and 3TC were evaluated when each drug was administered alone or when any two or three drugs were administered concurrently. No clinically significant pharmacokinetic interactions occurred between ABC, ZDV, and 3TC. No increase in adverse events with the three-drug combination were seen.

CNA2001 was a multicenter trial comparing the safety and efficacy of four doses of ABC alone and in combination with ZDV (Table 5) (99). Patients were randomized to four different ABC doses for the first 4 wk, and, thereafter, to combination therapy with 300 mg ABC twice daily and ZDV or placebo for 8 wk. At week 12, the percentages of patients with plasma HIV-1 RNA levels less than 400 and less than 40 copies/mL for ABC monotherapy were 28% and 11%, respectively, vs 69% and 22% for ABC plus ZDV. Median CD4 cell counts increased by 79 to 195 cells/mm³ and 93 to 142 cells/mm³ for ABC monotherapy and ABC plus ZDV, respectively, but these differences were not significant. Eight subjects (10%) discontinued the study prematurely because of adverse events, three with hypersensitivity reactions. After 12 wk on study, 72 of 79 patients were required to interrupt ABC treatment until essential pre-clinical studies were completed. In the extension phase of the trial, 43 of 72 subjects elected to restart open-label ABC therapy in combination with either an NNRTI or a PI after up to 1 yr of interruption (100). After 48 wk of therapy, more than 50% of patients receiving either nucleoside-only therapy or PI-containing therapy with ABC had an HIV RNA level less than 400 copies/mL.

Staszewski et al. reported results of a dose-ranging trial to evaluate the safety and efficacy of ABC alone or in combination with ZDV and 3TC in antiretroviral-naïve subjects (101). Patients were randomized to three ABC doses for 24 wk, after which subjects could switch to open-label 300 mg ABC twice daily, with ZDV and 3TC or other antiretrovirals as determined by their physician for an additional 24 wk. At week 4, the subjects in the 300 or 600 mg ABC groups had greater reductions in plasma HIV-1 RNA (median changes -1.55 and $-1.61 \log_{10}$ copies/mL, respectively) than patients in the 100 mg ABC twice-daily group (median change, $-0.63 \log_{10}$ copies/mL). Differences between the 300 and 600 mg twice-daily ABC groups were not significant. At week 48, a median reduction in plasma HIV-1 RNA of $2.8 \log_{10}$ copies/mL from the baseline of pooled ABC-treated subjects was seen. Sixty-five percent and 43% of patients had less than 400 and less than 50 HIV-1 RNA copies/mL, respectively, after 48 wk of ABC-containing therapy. A hypersensitivity reaction attributable to ABC was seen in 3.3% of patients.

ZDV Plus 3TC Plus ABC Vs ZDV Plus 3TC Alone in Antiretroviral-Naïve Adults

CNA3003 investigated the safety, tolerance, and antiviral activity of ZDV plus 3TC plus ABC at 16 and 48 wk. This multicenter trial of therapy-naïve

Table 5
Clinical Trials of Abacavir Combination Therapy

Trial (ref.)	Design	Dosage	No. of subjects	Entry criteria
CNA2001 (99)	Randomized, double-blind; ABC alone for 1st 4 wk, then ABC+ZDV or placebo for 8 wk	ABC 200 mg, 400 mg, or 600 mg TID; 300 mg BID; ZDV 300 mg BID	79	<12 wk ZDV
CNAB2002 (101)	Randomized, double-blind; ABC alone for 24 wk, then open-label ABC+ZDV+3TC or other NRTIs per physician	ABC 100 mg, 300 mg, or 600 mg BID; ABC 300 mg BID + ZDV 300 mg BID + 3TC 150 mg BID	60	VL \geq 30,000 copies/mL; CD4 \geq 100 cells/mm ³
CNAA3003 (102)	Randomized, double-blind; ZDV+3TC vs ZDV+3TC+ABC for 16 wk, then open-label ZDV+3TC+ABC	ZDV 300 mg BID; 3TC 150 mg BID; ABC 300 mg BID	173	Treatment naive; CD4 \geq 100 cells/mm ³
CNA3014 (103)	Randomized, double-blind; ABC+COM vs IDV+COM	ABC 300 mg BID, IDV 800 mg TID	342	Treatment naive; HIV RNA 5-100K
CNAF3007 (104)	Randomized, open-label; COM+ABC vs COM+NFV for 48 wk	ABC 300 mg BID, NFV 1250 mg TID	196	Treatment naive; HIV RNA 1000–500,000 copies/mL
ACTG 5095 (105)	Randomized, double-blind ZDV+3TC+ABC vs ZDV+3TC+EFV vs ZDV+3TC+ABC+EFV	ZDV+3TC/FDC (Combivir); ZDV+3TC+ABC/FDC (Trizivir); EFV 600 mg QD	167	Treatment naive
CNA3002 (107)	Randomized, double-blind; addition of ABC vs placebo to stable regimen	ABC 300 mg BID	185	CD4 >100 cells/mm ³ ; VL 400–500,000 copies/mL
CNAA3017 (108)	Open-label switch study; continue PI-based regimen vs switch to ABC-based regimen	ABC 300 mg BID	211	Stable PI-based regimen; HIV RNA <50 copies/mL

Table 5 (Continued)

Duration of follow-up	CD4 response (cells/mm ³)	Antiviral response	Comments
12 wk	ABC alone, 79–195; ABC+ZDV, 93–145	VL < 400 copies/mL: ABC, 28%; ABC+ZDV, 69%; VL < 40: ABC, 11%; ABC+ZDV, 22%	10% of subjects discontinued study prematurely for adverse events
48 wk	At week 24: ABC 100 mg, +26; ABC 300 mg, +97; ABC 600 mg, +40 At wk 48: median +111 pooled Median ZDV+ 3TC+150 ZDV+3TC+ABC +152	At week 24, mean log ₁₀ copies/mL change: ABC 100 mg, -0.63 ABC, 300 mg/600 mg: -1.55–1.61 At wk 48, pooled ABC median VL reduction, 2.8 VL < 400: ZDV+3TC, 35%; ZDV+3TC+ABC, 75%	All ABC doses well-tolerated, 2 subjects with hypersensitivity reaction
48 wk	Not reported	VL < 400: ABC plus COM 64%; IDV plus COM 50%	Loss of virological response and difficulty with regimen more common in IDV group
48 wk	Mean increase: COM+ABC, 109; COM+NfV, 120	VL < 50: COM+ABC, 64%; COM+NfV, 61%	Increased continuation of regimen and self-reported adherence in ABC group ABC+COM comparable antiviral activity to IDV+COM
Median 32 wk	Mean increase: ABC arm, +174; pooled EFV, +173	Virological failure: ABC arm 21% vs pooled EFV 11% (<i>p</i> < 0.001)	Interim results resulted in triple-NRTI arm termination
16 wk	ABC +30; stable regimen + 1 (intent to treat)	VL < 400: ABC 39%; stable regimen 8%	Antiviral response seen despite M184V mutation
48 wk	Cont PI arm +13; ABC arm +26 (intent to treat)	Virological failure continued PI 23%; ABC 12%	Significant reductions in cholesterol and triglyceride in ABC arm

^aQD, once daily; BID, twice daily; TID, three times daily; VL, viral load; Cont, continued

patients randomized subjects to ZDV plus 3TC plus ABC vs ZDV plus 3TC (102). Subjects were stratified by baseline HIV-1 RNA level: less than 10,000 copies/mL; 10,000 to 100,000 copies/mL; or more than 100,000 copies/mL. At week 16, all patients had the option to switch to open-label ABC plus ZDV plus 3TC. Patients with confirmed plasma HIV-1 RNA levels greater than 400 copies/mL were permitted to switch to a new regimen to include ABC and other available antiretroviral agents. In an intent-to-treat analysis at week 16, 75% and 35% of subjects in the ABC plus ZDV plus 3TC and ZDV plus 3TC groups, respectively, had an HIV-1 RNA level less than 400 copies/mL. The triple combination was effective at all HIV-RNA strata, whereas the dual-therapy group had a diminished virological response with a higher baseline HIV-1 RNA level. The mean increase in CD4 counts was similar between the treatment groups at 16 wk. There was no difference in tolerance between the two groups.

Triple-Combination Therapy: ABC Vs PIs

CNA3014 compared the efficacy, safety, and adherence of ABC plus COM (300 mg ZDV and 150 mg 3TC twice daily) vs IDV plus COM in 342 antiretroviral therapy-naïve patients (103). Subjects were stratified based on screening HIV-1 RNA levels (stratum 1, 5000–100,000 copies/mL; stratum 2, >100,000 copies/mL). At week 48, by intent-to-treat analysis, 105 of 164 (64%) ABC plus COM subjects vs 82 of 165 (50%) IDV plus COM subjects had an HIV-1 RNA level less than 400 copies/mL. Time-to-treatment failure during 48 wk was significantly longer for the COM plus ABC group than for the COM plus IDV group. For stratum 1 and 2, the values were 73 of 106 (69%) and 32 of 58 (55%), respectively, for ABC plus COM subjects vs 49 of 100 (49%) and 33 of 65 (51%) for IDV plus COM subjects. Eleven percent of ABC plus COM subjects vs 13% of IDV plus COM subjects discontinued randomized study therapy because of an adverse event. Ten (6%) ABC plus COM subjects reported possible hypersensitivity to ABC. Self-reported adherence to randomized treatment was significantly higher in the ABC plus COM group.

The CNAF3007 study evaluated the antiviral activity of COM plus ABC vs COM plus NFV in antiretroviral-naïve adults (104). In this randomized, open-label study, 196 patients with HIV-1 RNA levels of 1000 to 500,000 copies/mL were followed for 48 wk. Baseline viral loads were comparable in the two treatment groups. In the intent-to-treat analysis at 48 wk, 64% and 61% of subjects had HIV-1 RNA levels of less than 50 copies/mL in the COM plus ABC and COM plus NFV arms, respectively. The COM plus ABC group had median CD4 cell count increases of 109 cells/mm³, as compared with 120 cells/mm³ in the COM plus NFV group. Possible hypersensitivity reactions to ABC were seen in 4% of subjects.

Triple-Combination Therapy—ABC Vs EFV

ACTG 5095 was a comparative study of three PI-sparing antiretroviral regimens in treatment-naïve patients (105). Subjects were randomized 1:1:1 to ZDV plus 3TC plus ABC (FDC); ZDV plus 3TC (FDC) plus EFV; or ZDV plus 3TC plus ABC (FDC) plus EFV to assess safety and virological responses. Virological failure was defined as a confirmed HIV-1 RNA levels greater than 200 copies/mL more than 16 wk after randomization. Based on a planned interim review, the Data and Safety Monitoring Board recommended termination of the ZDV plus 3TC plus ABC arm. One hundred sixty-seven patients reached protocol-defined virological failure: 82 (21%) on ZDV plus 3TC plus ABC and 85 (10%) on pooled EFV arms. Time-to-virological failure was shorter with ZDV plus 3TC plus ABC compared with pooled EFV arms ($p < 0.001$). This trial suggested that ZDV plus 3TC plus ABC was inferior to EFV-containing regimens regarding virological failure in treatment-naïve patients.

ABC Expanded Access Program

The ABC Expanded Access Program was an international, multicenter, non-randomized, open-label study (106). In part A of the Expanded Access Program, all 2580 patients had a plasma HIV-1 RNA level greater than 30,000 copies/mL, a CD4 cell count of fewer than 100 cells/mm³, and virological failure to standard antiretroviral therapy that included at least two NRTIs and a PI. Part B enrolled 11,624 patients and required only that patients have infections that did not respond to standard therapy and that their providers' could not construct a viable treatment regimen without ABC. In both parts A and B, ABC was included as a component in a treatment regimen that contained at least one other antiretroviral drug that the patient had not received in the past. Virological analysis was performed only for Part A patients. By month 2 of the ABC-containing treatment, plasma HIV-1 RNA levels decreased by at least 0.5 log₁₀ copies/mL in 31.4% of patients, and 5.6% of patients had a decrease in HIV-1 RNA levels to less than 400 copies/mL. Drug-related serious adverse events were reported by 7.7% of patients, and 4.6% of patients experienced a hypersensitivity reaction that was possibly drug related.

ABC Addition to Stable Background Therapy

Katlama et al. reported the results of CNA3002, which evaluated the addition of 300 mg ABC twice daily vs placebo to a stable background antiretroviral regimen (SBG) (107). One hundred eighty-five patients with CD4 cell counts greater than 100 cells/mm³ and an HIV-1 RNA level of 400 to 50,000 copies/mL were randomized. Median plasma HIV-1 RNA level at entry was 3.68 log₁₀ copies/mL and 3.53 log₁₀ copies/mL for the ABC plus SBG and SBG groups, respectively. The proportion of subjects with up to 18 mo of previous

NRTI therapy and previous 3TC usage was similar in both treatment groups. The most frequent background regimens were 3TC plus ZDV (36%), two NRTIs plus a PI or NNRTI (21%), d4T plus 3TC (19%), and ZDV plus ddI (10%). At week 16, 36 of 92 (39%) vs 7 of 93 (8%) patients in the ABC plus SBG and SBG groups had an HIV-1 RNA level less than 400 copies/mL. A similar response was observed in both 3TC-naïve and 3TC-experienced subjects. Seventy-three percent of patients with the M184V mutation alone had a greater than 1 log₁₀ copies/mL reduction in plasma HIV-1 RNA level or had less than 400 copies/mL by week 16. The presence of three or more thymidine analog mutations with or without the M184V mutation was associated with reduced activity of ABC plus SBG.

Simplification With ABC-Based Triple Nucleoside Regimen Vs Continued PI Therapy

CNA30017 was an open-label, multicenter study in which 211 patients who had been on a stable highly active antiretroviral therapy regimen with two NRTIs plus one PI for at least 6 mo and had a plasma HIV-1 RNA level less than 50 copies/mL were randomized to replace the PI with ABC or to continue the same regimen (108). A significantly longer time-to-treatment failure was demonstrated in the ABC arm compared with patients who continued the same regimen, and more treatment failures were seen in the PI arm (23%) than the ABC arm (12%). A significant reduction in cholesterol and nonfasting triglyceride was demonstrated in the ABC arm. The incidence of treatment-related adverse events was not significantly different between treatment groups, although the number of adverse events resulting in discontinuation of randomized medication was higher in patients remaining on a PI (14% vs 8%).

ABC Pediatric Trials—Phase I

In ACTG 330, 47 HIV-infected children discontinued previous antiretroviral therapy and were orally administered 4 mg/kg ABC every 12 h for 6 wk, followed by 8 mg/kg ABC every 12 h for 6 or 12 wk (109). At a dose of 8 mg/kg every 12 h, the AUC for plasma concentration vs time and the plasma half-life values were comparable to those reported for adults receiving ABC at a dose of 300 mg twice daily. One case each of hypersensitivity reaction and peripheral neuropathy occurred during ABC monotherapy. Three children developed neutropenia while receiving ABC in combination with another antiretroviral agent. Mean CD4 cell count and plasma HIV-1 RNA level did not change when previous antiretroviral therapy was changed to ABC monotherapy.

Pediatric ABC Combination Therapy

CNAA3006 was a randomized, double-blind trial of ABC plus 3TC plus ZDV vs 3TC plus ZDV in antiretroviral-experienced HIV-infected children (110).

Two hundred five children with CD4 cell counts of at least 100 cells/mm³ were randomized to receive 8 mg/kg ABC twice daily plus 4 mg/kg 3TC twice daily plus 180 mg/m² ZDV twice daily; or only 3TC plus ZDV. In an intent-to-treat analysis at week 48, the proportion of patients with plasma HIV-1 RNA levels less than 10,000 copies/mL were 36% and 26% for the ABC plus 3TC plus ZDV and 3TC plus ZDV groups, respectively. Three percent of children experienced ABC-related hypersensitivity reactions.

In PENTA-5, antiretroviral-experienced children were randomized to three NRTI regimes with or without NFV (*111*). At 48 wk, the ABC-containing regimens with or without NFV resulted in the greatest HIV-1 viral load reduction.

ABC Resistance

ABC selects for several mutations on the reverse transcriptase gene, including M184V, K65R, L74V, and Y115F. The M184V mutation alone does not lead to significant ABC resistance. Clinical trials indicate that resistance to ABC is associated with the presence of the M184V mutation in combination with at least three thymidine analog mutations (*112*). Mutations at codons 65, 74, and, possibly, 184 lead to cross-resistance to ddI and ddC. Each of these mutations results in a twofold to fourfold decrease in susceptibility to ABC.

Drug Interactions

Very few drug interactions with ABC and other medications exist. The co-administration of ABC and ethanol increases the ABC AUC by 41% and the ABC half-life by 26% (*113*). Ethanol pharmacokinetics were unchanged.

Current Clinical Uses

Dosing and Formulations

ABC is supplied as 300 mg tablets and as an 20-mg/mL oral solution. The recommended daily dosage is 600 mg either once daily or in two divided doses for adults and 8 mg/kg twice daily (up to a maximum dose of 600 mg daily) for adolescent and pediatric patients 3 mo to 16 yr of age.

Trizivir™ is the only three-drug fixed-dose coformulation of antiretroviral medications and was approved for use in adults and adolescents weighing more than 40 kg in November 2000. Each Trizivir tablet contains 300 mg ABC, 150 mg 3TC, and 300 mg ZDV. One Trizivir tablet was bioequivalent to one 300-mg Ziagen tablet, one 150-mg Epivir tablet and 300-mg Retrovir tablet after single-dose administration to 24 fasting healthy subjects (*115*). The recommended oral dosage of Trizivir is one tablet twice daily. Because it is a fixed-dose tablet, Trizivir should not be prescribed for patients requiring dosage adjustment, such as those with creatinine clearances less than 50 mL/min or those experiencing dose-limiting adverse events.

Fischl et al. reported results of an open-label, randomized study of the efficacy of COM plus ABC compared with Trizivir (116). One hundred eighty-six subjects were on previous therapy with COM and ABC twice daily with or without a PI or an NNRTI and had an HIV-1 RNA level less than 400 copies/mL and a CD4 cell count greater than 200 cells/mm³. Patients were randomized to continue COM plus ABC or switch to Trizivir. Prestudy PI or NNRTI was continued if applicable. At 24 wk, 30 of 34 (88%) and 27 of 34 (79%) subjects had an HIV-1 RNA level less than 400 copies/mL and less than 50 copies/mL, respectively, in the COM plus ABC group as compared with 33 of 34 (97%) and 28 of 34 (82%) in the Trizivir group.

Toxicity

The most common side effects seen during ABC therapy are gastrointestinal and neurological side effects. The gastrointestinal side effects include nausea, vomiting, and diarrhea, and tend to abate after the first few weeks of ABC therapy. Dizziness, headache, malaise, and insomnia are the most common neurological side effects.

A hypersensitivity reaction to ABC has been reported in 3 to 7% of patients and is characterized by multisystem involvement. Symptoms usually appear within the first 6 wk of treatment, with a median time to onset of 11 d. Manifestations include fever, rash, gastrointestinal symptoms, myalgias, and lethargy. Less common symptoms include cough, dyspnea, and arthralgias. Symptoms worsen with continued therapy and usually improve within 24 h of ABC discontinuation. Use of prednisolone does not prevent ABC hypersensitivity and may increase the risk of this reaction (117). Rechallenge with ABC after development of hypersensitivity-related symptoms typically results in recurrence of symptoms within hours, with the potential to induce a more severe clinical syndrome, with increased risk of life-threatening hypotension and death. The mechanism of the ABC hypersensitivity reaction is not known, but clinical symptoms suggest an immunological reaction influenced by genetic factors. An association between development of ABC hypersensitivity and certain human leukocyte antigen haplotypes has been reported, although results are conflicting (118,119).

Current Uses

ABC is indicated for treatment of adults and children with HIV-1 infection in which treatment is indicated. The use of ABC as part of an initial therapy for antiretroviral-naïve patients is attractive from the standpoint of pill burden and potency when combined with a second NRTI and an NNRTI. ABC is currently recommended as part of an alternative initial regimen containing 3TC and EFV (87). The use of the three-NRTI regimen of ABC plus ZDV plus 3TC as an initial therapy has been associated with virological failure and, as such, is recommended for use only in patients in whom an NNRTI or a PI cannot be used. In addition,

the combination of ABC plus tenofovir plus 3TC should not be used as the sole combination at any time, based on data showing early virological nonresponse (120). ABC is a useful component of salvage therapy in patients without HIV isolates resistant to multiple nucleoside compounds.

SUMMARY

The discovery and development of the antiretroviral agents ZDV, 3TC, and ABC has lead to widespread reductions in morbidity and mortality for persons infected with HIV. From the use of these agents as monotherapy, followed by their combination together and with other nucleoside analogs to form the “nucleoside backbone” of triple-combination therapy, these agents have become some of the most commonly prescribed antiretroviral medications. The development of the coformulation of ZDV plus 3TC as COM, and of ZDV plus 3TC plus ABC as Trizivir, along with the once-daily dosing formulation of 3TC have been exciting additions to the armamentarium of antiretroviral medications, with obvious adherence implications. The capacity for use of 3TC for treatment of HIV-1 and hepatitis B, along with its exceptional toxicity profile and ease of dosing, have made 3TC particularly attractive for initial regimens. Finally, in a once-daily dose, the coformulation of 3TC plus ABC represents a future direction for these agents.

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