

CLINICAL REVIEW

3TC: A Canadian Scientific Success Story

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THE DISCOVERY OF 3TC

The epidemic of acquired immune deficiency syndrome (AIDS) has prompted a broadly based effort to find means of preventing and treating this disease. Enzymes that are unique to human immunodeficiency virus (HIV) catalyze a number of essential steps in the life cycle of the virus. In 1987, when BioChem Pharma (Laval, Quebec, Canada) initiated a research program in AIDS, some agents had been reported to inhibit the replication of HIV. Among the most potent of these were 2'3'-dideoxynucleoside analogues targeted against the viral reverse transcriptase (RT), an enzyme used by HIV to replicate. In cell culture, the most active were dideoxycytidine (ddC) and 3'-azido-3'-deoxythymidine (AZT). The latter was approved for the therapy of AIDS in March 1987.

Nevertheless, it was known that therapy with AZT was associated with significant side effects. In particular, bone marrow suppression and subsequent anemia were observed. Also, clinical trials with ddC had demonstrated the development of painful peripheral neuropathy in patients treated with this drug, hence limiting its use as a therapeutic agent for the treatment of AIDS. It was thus clear that drugs with antiviral activities equivalent or superior to those of AZT and ddC, but with lower toxicities, should be sought for the treatment of HIV-infected individuals.

Considering this important need, the late Dr. Bernard Belleau, formerly from McGill University (Montreal, Quebec, Canada), with his team of chemists and with scientists from BioChem Pharma, initiated in 1987 a research program directed toward the discovery of novel nucleosides analogues aimed at inhibiting RT. An analysis of stereochemical and electronic parameters

led to the conclusion that the activity and specificity of nucleoside analogues as inhibitors of RT are dependent on the shape of the deoxyribose ring as well as the electronic environment in the C-3' region. Therefore, Dr. Belleau and the BioChem Pharma team designed and synthesized nucleoside analogues with an isosteric pentose ring in which the 3'-carbon was replaced by a heteroatom.

The rationale behind this novel modification was that the electron lone pair of the heteroatom at 3'-carbon would be involved in hydrogen bond formation between atoms of the enzyme's catalytic site so that the nucleoside analogues would bind more to the enzyme. This type of modification would then simulate the effect of the hydroxyl group present on the natural deoxynucleoside building blocks.

Among the novel compounds synthesized, one was found to be very potent at inhibiting the replication of HIV *in vitro* by Dr. Mark Wainberg at the Lady Davis Institute of the Jewish General Hospital (Montreal, Quebec, Canada). The compound was the racemic 2'-deoxy-3'-thiacytidine (BCH-189; also known as 3TC), a nucleoside analogue in which the ribose was replaced by a 1,3-oxathiolane ring (1). The sugar ring was novel in that the 3'-carbon of the ribose ring of 2'-deoxycytidine (ddC) had been replaced by a sulphur atom. The molecular structure is shown in Figure 1.

BCH-189 was a racemic mixture of the natural β -D(+) and the non-natural β -L(-) enantiomers. All previously known biologically active nucleoside therapeutic agents possessed the natural or β -D(+) sugar configuration. That nucleoside analogues possessing the "non-natural" β -L(-) configuration should exert any biological activity came as a great surprise. A paradigm shift occurred towards the acceptance of selective viral enzyme inhibition as a minimum standard for a viable treatment of human viruses. This concept was first

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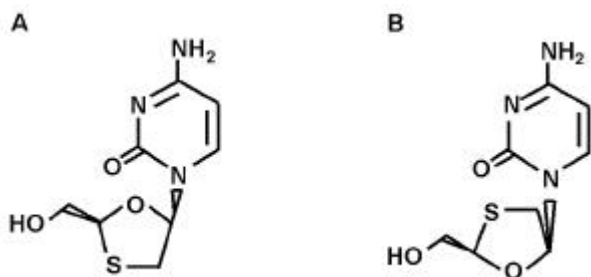


Figure 1. The molecular structure of 2'-deoxy-3'-thiacythine (BCH-189). **A:** (+)-Enantiomer. **B:** (-)-Enantiomer (3TC).

demonstrated when the β -D(+) and β -L(-) enantiomers of BCH-189 were found to be equipotent against the HIV, the causative agent of AIDS (2). However, only the β -D(+) enantiomer inhibited the constitutive human DNA polymerases responsible for the toxicity associated with nucleoside drugs. In contrast, the β -L(-) enantiomer, 3TC, was remarkably free from toxicity associated with polymerase inhibitors (3). Thus, 3TC differs stereochemically from the other members of the family of nucleoside analogues in that it is a negative enantiomer, in which the ribose ring is "flipped" compared with physiologic nucleosides, while AZT, d4T, ddI and ddC are positive enantiomers.

MECHANISM OF ACTION

RT is a multifunctional enzyme that is essential for the replication of HIV. The relevance of RT as a therapeutic target stems from the fact that no cellular homologues have been identified to date. Among the HIV-RT inhibitors, AZT was the first to show a clinical benefit. The central question was not whether antiretroviral activity was feasible, but rather, how to achieve selectivity toward the viral target. Excellent selectivity has been achieved by controlling the absolute stereochemistry of the acetal centers of the surrogate ribose ring in order to obtain exclusively the β -L(-) enantiomer.

3TC enters the cell by non-facilitated passive diffusion. As with other nucleoside analogues, 3TC is not active as the administered compound, but requires intracellular triphosphorylation by human cellular kinases to its active form 3TC triphosphate. This then competes with 2'-deoxycytidine-5'-triphosphate, the natural substrate of viral RT, and human cellular DNA polymerases, for inclusion in the growing DNA chain. Absence of the hydroxyl (-OH) group at the 3'-position of the ribose ring means a new 3'-5'-phosphodiesterase bond cannot be formed with the next nucleoside, hence the further extension of the DNA strand is prevented. 3TC is therefore both a competitive inhibitor of RT and a DNA chain terminator.

RESISTANCE

3TC rapidly selects for resistant virus both *in vitro* and *in vivo*. A substitution of methionine at codon 184 for either valine or isoleucine (most commonly M184V, less commonly and usually transiently, to Ile) (4-10) is observed during both combination and monotherapy. The M184V substitution was initially observed by Wainberg and co-workers (8).

Given the substantial change in viral sensitivity with the appearance of 3TC resistance, it is surprising that the viral load in persons receiving 3TC monotherapy does not rapidly return to baseline (4,6). Although some loss of virological response is observed at the same time as appearance of the valine mutation at codon 184, the persistence of viral load levels below baseline is observed during both monotherapy and combination studies. In patients stopping 3TC therapy after prolonged periods a rebound in viral load of around 0.5 log is observed (11). It has been suggested that these observations may relate to the functional compromise placed on RT by this mutation (4,12). Codon 184 lies in a highly conserved region of RT, known as the YMDD motif, adjacent to the catalytic site (9) and thus may influence RT function resulting in virions with impaired replication. Studies have confirmed the importance of residue 184 of RT mutants in generating replication deficient viruses. In primary peripheral blood mononuclear cells (PBMC), these viruses show a reduced fitness (hence replication efficiency) compared with wild type (13). Reduced replication rate may explain some of the beneficial effects of both 3TC monotherapy and 3TC in combination with other inhibitors (14,16). Also, it has been suggested that valine at codon 184 may enhance the fidelity of RT (6).

RATIONAL FOR THE DEVELOPMENT OF 3TC

It was clear from preclinical studies that 3TC had a wide therapeutic index. This enabled rapid progression of this agent into clinical studies. Studies in mouse, rat, dog and marmoset demonstrated that both oral and intravenous 3TC was well tolerated. Subchronic (up to 90 days) dosing studies in the rat showed doses up to 4000mg/kg/day resulted in only minor changes to hematological, blood and urinary chemical profiles. No teratogenic potential has been observed in the rat at doses up to 4000mg/kg/day. Also, no evidence of genetic toxicity has been observed.

3TC possesses favorable pharmacokinetics in man with a high, non-food-dependent, oral bioavailability and a relatively long intracellular half-life of the active form. The absolute bioavailability is 86%, with a rapid median absorption time of 1.32 hours (17). The mean systemic clearance ranged from 21.6 - 26.0 l/h with 49-85% of the dose being excreted unchanged in the urine (18).

3TC penetrates the cerebrospinal fluid (CSF), with the CSF/plasma ratio being time dependent. In a pilot study, combinations of 3TC with either AZT or d4T resulted in CSF HIV RNA load in all 28 patients falling below assay detection limits (19). Significant drug interactions have not been reported with 3TC. Binding of 3TC to plasma proteins is concentration-dependent with moderate (35-50%) binding at concentration of substrate below 0.1µg/mL. Studies have shown that 3TC is active *in vitro* against both HIV-1 and HIV-2, that it has potent activity against AZT-resistant strains and that it acts synergistically with AZT *in vitro*. In addition, inhibition of DNA polymerase gamma, which is assumed to be associated with the peripheral neuropathy observed with ddC and ddI, is minimal with 3TC (3). 3TC is metabolized intracellularly to 5' mono-di-and triphosphate; the latter active metabolite has been shown to have a long intracellular half-life of between 11 and 14 hours in infected cells (20).

THE 3TC CLINICAL DEVELOPMENT PROGRAM

Surrogate Markers Studies

Initial phase I studies (21) were followed by the initiation in mid-1991 of two phase I/II dose-ranging monotherapy studies in Europe and North America (22,23). Based on the pharmacokinetic profile, an initial dosing interval of 12 hours was selected. Analysis of the change in surrogate markers supported the antiviral activity of 3TC. Also, the results showed that 3TC was well tolerated and no significant side effects attributable to the medication were observed.

The combination of 3TC with AZT has demonstrated efficacy in pivotal Phase II/III clinical trials. Four randomized, controlled, double-blind trials (two conducted in North America and two in Europe) assessed the efficacy of 3TC in combination with AZT in adult HIV-infected patients using surrogate markers (i.e., immunologic and viral markers) of disease progression (15,24-26). Two of these trials (one in each continent) were conducted as initial therapy for antiretroviral therapy-naïve patients (15,24) and two were conducted in the antiretroviral-experienced population (25,26). The prognostic clinical value of immunological markers (e.g., CD4 cell count) and, in particular, virologic markers (e.g., HIV RNA – viral load) in patients with HIV disease has become more widely accepted, and data strongly support the utility of these markers in predicting the clinical benefit associated with antiretroviral therapy (27). The use of surrogate markers is a standard measure of the success of HIV therapies and they enable treatments in development to be quickly approved and become available to those in need. The results of these four

surrogate markers clinical trials were highly consistent, each demonstrating that combination therapy of 3TC/AZT produces the most marked and prolonged increases in CD4 cell counts and reductions in plasma viral load compared with AZT monotherapy or any other two-drug combination available. In addition, 3TC was shown to be remarkably well tolerated with a side-effect profile uniquely characterized as mild.

Clinical End Point Studies

However impressive these phase II/III clinical trials results were, there was still no conclusive proof that the superior responses of surrogate endpoints observed with 3TC/AZT would translate into meaningful therapeutic clinical benefits over existing treatments for patients with HIV infection. To this end two large clinical end point studies have clearly indicated that addition of 3TC (with or without other agents) to on-going therapy improves clinical outcome. First, an international clinical end point study known as CAESAR – an acronym of the countries involved (Canada, Australia, Europe, South Africa) – was initiated in January 1995 to determine the true effect of the combination of 3TC/AZT on the clinical progression of HIV/AIDS (28). This study involving 1,892 HIV-infected patients (baseline CD4: 25-250 cells/mm³) investigated the clinical efficacy of adding either placebo, 3TC or 3TC plus zalcitabine (an investigational antiviral drug from Janssen) to the patient's existing background anti-HIV treatment (either AZT, AZT/ddI or AZT/ddC). The primary outcome was progression to a new AIDS diagnosis or death. All patients were scheduled to remain on blinded treatment for 52 weeks.

In July 1996, Glaxo Wellcome and BioChem Pharma released interim results from CAESAR. Compared with placebo, the benefits of adding 3TC to a current therapy regimen was demonstrated by a striking 57% reduction ($p < 0.0001$) in the rate of HIV/AIDS disease progression or death. The addition of 3TC also resulted in a significant survival benefit of 53% ($p = 0.0115$). These results were sufficiently compelling to prompt an independent Data and Safety Monitoring Board, on ethical grounds, to recommend the early termination of the study, originally scheduled to end in March 1997, to allow patients still on blinded treatment immediate access to 3TC.

In CAESAR the addition of 3TC to AZT containing regimens did not result in any significant increase in the frequency and severity of adverse events or laboratory abnormalities. Only 3% of patients discontinued due to an adverse event.

More recently, the ACTG 320 study has indicated that the addition of 3TC/indinavir is superior to the addition of 3TC alone to ongoing AZT therapy (29). This study involved 1,156 3TC/protease inhibitor-naïve, AZT-

experienced patients randomized in a double-blind placebo controlled manner to add 3TC or 3TC plus indinavir (800mg three times daily). In patients unable to tolerate AZT, d4T was substituted. The study included patients with < 200 CD4 cells/mm³ (mean 87 cells/mm³) and baseline viral loads of 5.0 log₁₀. The median duration of follow-up was 38 weeks over which time 96 disease progressions or deaths had occurred; 63 in the dual therapy and 33 in the triple therapy groups. This represented a reduction in the relative hazard of disease progression or death of 50% (95% confidence interval 0.33-0.76) for triple therapy.

Safety and Tolerability

3TC was administered to a total of 972 HIV-infected adults (15,24-26) and 144 HIV-infected children (30,31) in the controlled phase II and III clinical trials program. Safety data collected from these trials revealed no new or unexpected adverse events for nucleoside analogues with 3TC or any of its combinations. Importantly, the nature and frequency of adverse events reported with the combination of 3TC plus AZT was similar to that associated with the use of AZT monotherapy and was favorable to that of AZT/ddC. The most frequent adverse events (~5%) reported during therapy with 3TC in combination with AZT were nausea, headache, malaise/fatigue, diarrhea, vomiting and dizziness. Peripheral neuropathy, commonly associated with other nucleoside analogues, was infrequently observed during treatment with 3TC.

3TC Safety: The Expanded Access Experience

Prior to the regulatory approval of 3TC in 1995, the largest expanded access/open-label program ever established was undertaken by Glaxo Wellcome to provide 3TC to patients who had failed, or were intolerant to, other approved antiretroviral therapies. This program provided early access to 3TC to a widespread and varied population in an open clinical practice community setting. In total, the program covered approximately 35,000 pediatric and adult patients with HIV infection world-wide, including over 2,900 HIV-infected patients in Canada. Presented in 1996 at the XI International Conference on AIDS (Vancouver, British Columbia, Canada) the extensive safety data collected on the use of 3TC/AZT from this program did not reveal any new or increased frequency of adverse events compared with those observed in controlled clinical trials, thus demonstrating that 3TC is well tolerated and has no additional adverse events compared with AZT monotherapy (32). This aspect of 3TC's profile is a key requirement of any new antiretroviral since combination drug therapy has become the standard approach to HIV treatment (33). A well-tolerated

safety profile is important to maintain patient compliance, drug efficacy and quality of life.

ADDITIONAL BENEFITS OF 3TC

The burden of HIV infection in both social and economic terms is immense. Both direct and indirect costs contribute to its impact with the cost of treating HIV infection and the use of healthcare resources increasing with disease progression. The major economic and personal impacts of AIDS are driven by opportunistic infections. A treatment that can avert opportunistic infections may also affect their impact. This may allow a longer and more productive life free from the burden of these infections.

Impact of 3TC on Quality of Life

HIV reduces life expectancy and erodes an individual's ability to work, to interact normally with others and to be independent. Each of these factors has a profound impact on the psychological and social aspects of an individual's quality of life. From an individual's perspective, health-related quality of life view with clinical efficacy and drug safety as the most important outcomes of treatment of HIV infection (34). The goals of HIV therapy should therefore include preservation of quality of life in individuals with HIV infection.

A quality-of-life (QOL) analysis conducted as part of the CAESAR study showed that 3TC recipients maintained their QOL levels whereas placebo recipients reported a significant decline in four of the 10 Medical Outcomes Study HIV Health Survey (MOS-HIV) subscales. Furthermore, a larger proportion of 3TC recipients was satisfied with their medication, compared with receiving placebo.

The QOL analysis involved 495 patients who completed the MOS-HIV questionnaire at outpatient HIV centers in Australia, Canada or the UK. Patients completed the MOS-HIV at baseline and during the follow-up visit (at 28 weeks or at the end of treatment). There were significant differences in the process for vitality, perceived health, and social and physical functioning, between 3TC and placebo recipients, favoring 3TC over placebo. Patients receiving 3TC maintained their physical and mental health summary scores whereas placebo recipients reported significant declines (35).

Cost-Effectiveness of 3TC Combination Therapy

In HIV/AIDS, opportunistic infections are responsible for the majority of treatment related costs. Several studies have shown a strong association between the acquisition of opportunistic infections and the CD4 cell count – the severity and incidence of opportunistic infections increases as CD4 cell counts

decrease. 3TC may defer opportunistic infections, improve survival and may, in turn, have an overall positive effect on the economic burden of infection.

An intent-to-treat evaluation of healthcare resource during the CAESAR study showed that the mean number of hospital admissions, hospital days, and unscheduled outpatient visits for HIV-related illness during the year decreased by 47%, 51% and 32%, respectively, in the 3TC group compared with the placebo group. Furthermore, 41% fewer 3TC recipients required other prescribed medication than placebo recipients. The mean number of hospitalizations for adverse events was 36% lower among 3TC recipients than among placebo recipients; a similar trend was seen for unscheduled outpatient visits. In the US substudy, cost savings associated with the reduction in resource use among 3TC recipients, compared with placebo recipients, totalled \$2,645(US)/patient over the year. Ninety-eight percent (\$2,592) of this amount was due to fewer hospitalizations. Therefore, in the US, 3TC therapy is associated with either lower costs and better outcomes, or higher costs and better outcomes, compared with placebo. In the other countries studied, namely Canada, UK and Germany, total cost savings with 3TC partially offset the acquisition of cost of the drug (35).

ROLE OF 3TC IN HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

Highly active antiretroviral therapy (HAART) has become the standard for controlling HIV infection. These triple or quadruple combinations involve nucleosides analogues, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI). Many positive results have been obtained from clinical trials involving the use of 3TC in combination with two other nucleoside analogues or with one other nucleoside analogue plus a protease inhibitor or with another nucleoside analogue plus a NNRTI. For example, recently, very promising results were presented for the combination 3TC/d4T/Sustiva (the latter being a recently approved NNRTI). Preliminary data were disclosed at the 9th Annual Conference of Clinical Microbiology and Infections Diseases (Berlin, Germany) in March 1999. The results suggest that 3TC, in combination with d4T and Sustiva is a very potent, tolerable and easy to take first-line option against HIV. It reduced viral load to less than 400 copies/mL in all patients using an as-treated analysis.

In the trial all patients – with average baseline viral load of 75.858 copies/ml and CD4+ counts of 380 cells/ml – received 600 mg/day of Sustiva, 30-40 mg of d4T twice daily and 150 mg of 3TC twice daily. Using an observed data analysis at 24 weeks, 97% achieved viral loads below quantifiable levels using an ultrasensitive assay (<50 copies/ml) and 100% of patients achieved viral loads below 400 copies/ml.

These new results suggest that this regimen is close to the optimum and are probably the best results obtained with HAART to date (36).

CONCLUSION

3TC has a number of advantages which make it an important agent in current anti-retroviral therapy. These include good antiviral activity, convenient dosing and excellent tolerability. 3TC's role in the management of HIV infection is as a combination agent, with the potential for combination with a range of other RT inhibitors, protease inhibitors and NNRTI. 3TC-based triple therapies have demonstrated very potent antiviral effects with a high proportion of patients achieving the virological goal of treatment: an undetectable viral load. Whilst no prospective comparative data exist, some physicians believe 3TC-containing regimens are the most potent available. This may explain why 3TC is currently the cornerstone of antiretroviral therapy and the world's most prescribed drug for the treatment of HIV infection and AIDS.

REFERENCES

1. Coates JAV, Cammack N., Jenkinson HJ et al. (-)2'-3'-thiacytidine is a potent, highly selective inhibitor of human immunodeficiency virus type 1 and type 2 replication in vitro. *Antimicrobial Agents and Chemotherapy* 36; 4:733-739; 1992.
2. Angel JB, Hussey EK, Hall ST, et al. Pharmacokinetics of 3TC administered with and without food to HIV-infected patients. *Drug Invest* 1993; 6: 70-74.
3. Hart GJ, Orr DC, Penn Cr, et al. Effects of (-)-2'-deoxy-3'-thiacytidine (3TC) 5'-triphosphate on human immunodeficiency virus reverse transcriptase and mammalian DNA polymerases alpha, beta and gamma. *Antimicrobial Agents and Chemotherapy* 36:1688-1694; 1992.
4. Schourman R., Nijhuis M., Van Leeuwen R., et al. Rapid changes in human immunodeficiency virus type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). *Journal of Infectious Diseases* 171: 1411-1419; 1995.
5. Kavlik MF, Shirasaka T., Kojima E., et al. Genotypic and phenotypic characterization of HIV-1 isolated from patients receiving (-)-2'-3'-dideoxy-3'-thiacytidine. *Antiviral Research* 28:133-146; 1995.
6. Wainberg MA, Drosopoulos WC, Salomon H, et al. Selected mutant HIV-1 reverse transcriptase. *Science* 271:1282-1284; 1996.
7. Tisdale M, Kemp SD, Parry NR, et al. Rapid in vitro selection of human immunodeficiency virus type 1 resistant to 3'-thiacytidine inhibitors due to a mutation in the YMDD region of reverse transcriptase. *Proceedings of the National Academy of Sciences, (USA)* 90:5633-5656; 1993.
8. Gao Q, Gu ZX, Parniak MA, et al. The same mutation that encodes low-level human immunodeficiency virus type 1 resistance to 2'-3'-dideoxyinosine and 2'-3'-dideoxycytidine confers high-level resistance to the (-) enantiomer of 2'-3'-dideoxy-3'-thiacytidine. *Antimicrobial Agents and Chemotherapy* 37:1390-1392; 1993.
9. Schinazi RF, Lloyd RJ, Nguyen M-H, et al. Characterization of human immunodeficiency viruses resistant to oxathiolane-cytosine nucleosides. *Antimicrobial Agents and Chemotherapy*

- 37:875-881; 1993.
10. Wainberg MA, Salomon H, Gu Z, et al. Development of HIV-1 resistance to (-)2'-deoxy-3'-thiacytidine in patients with AIDS or advanced AIDS-related complex. *AIDS* 9: 351-357; 1995.
 11. Eron JJ, St Clair M, Gilbert C, et al. Rebound of plasma HIV-1 RNA after discontinuation of long-term lamivudine/zidovudine. International Workshop on HIV Drug Resistance, Treatment Strategies and Eradication, St. Petersburg, Florida, USA. Abstract 97.
 12. Kemp SD, Harrigan PR, Kinghorn I, et al. Antiviral potency of AZT + 3TC combination therapy in vivo supports in vitro virological observations. *AIDS* 8 (Supplement 4): S20; 1995.
 13. Back NK, Nijhuis M, Keulen W, et al. Reduced replication of 3TC resistant HIV-1 variants in primary cells due to a processivity defect of the reverse transcriptase enzyme. *EMBO Journal* 15: 4040-4049; 1996.
 14. Shourman R, Nijhuis M, van Leeuwen R, et al. Rapid changes in human immunodeficiency virus type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). *Journal of Infectious Disease* 171:1411-1419; 1995.
 15. Eron JJ, Benoit SL, Jemsek J, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *New England Journal of Medicine* 333:1662-1669; 1995.
 16. Larder BA, Kemp SD and Harrigan PR. Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. *Science* 269; 696-9; 1995.
 17. Yuen GJ, Morris DM, Mydlow PK, et al. Pharmacokinetics, absolute bioavailability and absorption characteristics of lamivudine. *Journal of Clinical Pharmacology* 1995; 35: 1174-1180.
 18. Van Leeuwen R, Lange JMA, Hussey EK, et al. The safety and pharmacokinetics of a reverse transcriptase inhibitor, 3TC, in patients with HIV infection: a phase I study. *AIDS* 6:1471-1475; 1992.
 19. Foundraine N, Hoetelmanns R, de Wolf F, et al. HIV-RNA and drug levels in cerebrospinal fluid (CSF) after treatment with stavudine (D4T) or zidovudine (AZT) both in combination with lamivudine. 6th European Conference on Clinical Aspects and Treatment of HIV Infection, Hambrug, Germany, Abstract 250; 1997.
 20. Cammack N, Rouse P, Marr CL, et al: Cellular metabolism of (-) enantiomeric 2'-deoxy-3'-thiacytidine (3TC). *Biochemical Pharmacology* 43:2059-2064; 1992.
 21. Van Leeuwen R, Lange JMA, Hussey EK et al. The safety and pharmacokinetics of a reverse transcriptase inhibitor, 3TC, in patients with HIV infection: a phase I study. *AIDS* 1471-1475; 1992.
 22. Pluda JM, Cooley TP, Montaner JSG, et al. A phase I/II study of 2'-deoxy-3'-thiacytidine (lamivudine) in patients with advanced immunodeficiency virus infection. *Journal of Infectious Disease* 171: 1438-1447; 1995.
 23. Van Leeuwen R, Katlama C, Kitchen V, et al. Evaluation of safety and efficacy of 3TC (lamivudine) in patients with asymptomatic or mildly symptomatic human immunodeficiency virus infection: a phase I/II study. *Journal of Infectious Disease* 171:1166-1171; 1995.
 24. Katlama C, Ingrand D, Loveday C, et al. Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naive patients. A randomized controlled comparison with zidovudine monotherapy. *JAMA* 276:118-125; 1996.
 25. Bartlett JA, Benoit S, Johnson VA, et al. Lamivudine plus zidovudine compared with zalcitabine plus zidovudine in patients with HIV infection. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 125: 161-172; 1996.
 26. Staszewski S, Loveday C, Picazo JJ, et al. Safety and efficacy of lamivudine-zidovudine combination therapy in zidovudine-experienced patients. A randomized controlled comparison with zidovudine monotherapy. *JAMA* 276: 111-117; 1996.
 27. Phillips AN, Eron JJ, Bartlett JA, et al. HIV-1 RNA levels and the development of clinical disease. *AIDS* 10: 859-865; 1996.
 28. Montaner J, Cooper D, Katlama C, et al. CAESAR: Confirmation of the clinical benefit of 3TC (Epidur) in HIV-1 Disease: Preliminary results. Presented at the 36th ICAAC, New Orleans Louisiana, USA. LB6; 1996.
 29. Hammer SM, Squire KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *New England Journal of Medicine* 337: 725-733; 1997.
 30. Angel JB, Hussey EK, Hall ST, et al. Pharmacokinetics of 3TC administered with and without food to HIV-infected patients. *Drug Invest*: 6: 70-74; 1993.
 31. Van Leeuwen R, Lange JMA, Hussey EK, et al. The safety and pharmacokinetics of a reverse transcriptase inhibitor, 3TC, in patients with HIV infection: a phase I study. *AIDS* 6: 1471-1475; 1992.
 32. Conant M, Self P, Liao E, et al. Efavirenz (3TC) expanded access program – North American safety experience. The XI International Conference on AIDS, Vancouver British Columbia, Canada. LB.B:6032; 1996.
 33. Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1996. Recommendations of an international panel. *JAMA* 276:146-154; 1996.
 34. Wu AW, Mathews WC, Brysk LT, et al. Quality of life in a placebo-controlled trial of zidovudine in patients with AIDS and AIDS-related complex. *Journal of Acquired Immune Deficiency Syndrome* 3:683-690; 1990.
 35. Tood C. *PharmacoEconomics and Outcomes News*. 168: 27 July; 1998.
 36. *SCRIP* 2425: 16, April 2; 1999.

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