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GlaxoSmithKline LLC, erroneously sued herein as SmithKlineBeecham Corporation, dba GlaxoSmithKline, a Corporation

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF ALAMEDA

LISA ZAPATA, individually, and VERONICA ZAPATA and ZACHARY ZAPATA, by and through their GUARDIAN AD LITEM, GABRIEL REYNOSO,

Plaintiffs,

v.

LISHA WILSON, M.D., an individual; JOSEPH MARZOUK, M.D., an individual; SMITHKLINE BEECHAM CORPORATION, dba GLAXOSMITHKLINE, a corporation; DOE COMPANY, an unknown business entity; and DOES 1 through 50, inclusive,

Defendants.

No.: RG104945568

DECLARATION OF ALEXANDRA M. LEVINE, M.D. IN SUPPORT OF GLAXOSMITHKLINE LLC'S MOTION FOR SUMMARY JUDGMENT OR IN THE ALTERNATIVE FOR SUMMARY ADJUDICATION

I, ALEXANDRA M. LEVINE, declare:

1. The matters set forth in this Declaration are true and accurate based upon my own expertise and personal knowledge, unless otherwise indicated, and the opinions stated herein are provided to a reasonable degree of medical/scientific certainty. If called upon to do so, I could competently testify to the following:

2. I am a physician and a clinical researcher specializing in oncology and hematology, and in diseases associated with the Human Immunodeficiency Virus (HIV), most specifically in AIDS related malignancies, including lymphomas. I am the Chief Medical Officer, and Professor of Hematology at City of Hope National Medical Center which is one of only 40 National Cancer Institute (NCI) designated Comprehensive Cancer Centers in the US, and is known for the research and treatment of cancer, including AIDS related lymphoma. I was elected a Master of the American College of Physicians (MACP) in 2008.

3. The opinions and conclusions expressed in this declaration are based upon my decades of professional and research experience, as well as on the medical records and reports I have reviewed concerning this matter, and on the scientific and medical literature related to the subjects in question and on declarations of other scientists.

4. I graduated Phi Beta Kappa from the University of California at Berkeley in 1966, and received a Medical Degree from the University of Southern California in 1971. I did my internship at Los Angeles County and University of Southern California Medical Center (LAC-USC) in 1971-72 and my residency in Internal Medicine at LAC-USC in 1972-74. I then did a fellowship in Oncology at Emory University School of Medicine in Atlanta, Georgia in 1974-1975, and was a Clinical Research Fellow in Hematology at LAC-USC Medical Center in 1976 and 1977

5. During my career I have held a number of research and clinical positions in which I have studied cancers and infectious diseases, including those associated with Acquired Immunodeficiency Syndrome (AIDS), and I have treated thousands of patients with those illnesses. I was promoted to the rank of Professor of Medicine at USC School of Medicine in 1986 and later was designated as a Distinguished Professor of Medicine. From 1983 to 1997, I was the Deputy Clinical Director of the USC Norris Cancer Hospital and Research Institute. In 1996 and 1997 I was Interim Chief, Division of Medical Oncology, USC School of Medicine, and from 1991 to 2006 was Chief of the Division of Hematology at the Keck School of Medicine at USC ("USC"). I served as

the Executive Associate Dean of the USC School of Medicine between 1985-1990. From 1996-2006, I was the Medical Director of the USC Norris Cancer Hospital, where I was also the Chief of the Division of Hematology.

6. My practice has been divided between: (1) teaching medical students and graduate physicians and scientists; (2) clinical research involving lymphoma, HIV/AIDS and AIDS-related malignancies; (3) direct patient care of individuals with hematologic malignancies and/or HIV/AIDS; (4) administration at the USC Keck School of Medicine, or at City of Hope National Medical Center. Over the years, I have diagnosed and treated hundreds of patients with HIV/AIDS, and have prescribed AZT many hundreds of times.

7. My primary research interests include the definition of disease as it relates to lymphoproliferative malignancies (including the lymphomas), therapeutic protocols involving hematologic neoplasia, HIV/AIDS, and malignancies associated with HIV/AIDS. As such, I have personally participated in or supervised numerous *in vitro*, as well as human studies involving chemotherapeutic and anti-retroviral agents, as well as numerous epidemiological studies. As a principal investigator, I have received continuous funding from the National Institutes of Health (NIH) for over 25 consecutive years, including research funding from the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Development (NICHD), as well as the University-wide Task Force on AIDS from the University of California, the Untied States Public Health Service, and, in addition I have received numerous private grants for research in HIV/AIDS and AIDS-related lymphomas.

8. I was named Member and Chair of the Research Committee for the Presidential Advisory Council on HIV/AIDS by President Bill Clinton in 1996 and served in this capacity for 5 years. I have served on numerous international advisory panels concerning HIV/AIDS and AIDS-related cancers, including consulting appointments by the health ministries of China, Chile, India, and Russia. I serve on the Board of Scientific Councilors for the National Cancer Institute.

9. I have advised both the United States National Cancer Institute and the Food and Drug Administration (FDA) on matters related to cancer medications and treatments. In this respect I have been appointed to several Scientific Advisory Committees for the National Cancer Institute; as well as to the Oncologic Drug Advisory Committee of the Food and Drug Administration. and the Lymphoma, Leukemia, Myeloma Program Review Group of the National Cancer Institute.

10. I have also served on numerous national and statewide committees and advisory boards and study sections, including the Task Force on AIDS Malignancy for the National Cancer Institute, the Board of Directors of AIDS Project Los Angeles, the Program Committee for the American Society of Clinical Oncology, the Patient Advocacy Committee for the American Society of Clinical Oncology, the Advisory Committee for AIDS Fellowship for National Medical Fellowships, the Oncology Committee for the National AIDS Clinical Trials Group for NIAID (Chair), the Executive Committee and principal investigator for the NIH sponsored Women's Interagency HIV Study (Chair), and the AIDS Malignancy Working Group, sponsored by the NCI (chair).

11. I have served on the Editorial Advisory Board for numerous journals including Biotherapeutics and Cancer, Life Sciences, the Journal of the Acquired Immune Deficiency Syndrome and Hematologic Oncology. I have been a reviewer and consultant for numerous journals including, Blood, Annals of Internal Medicine, Journal of Clinical Oncology, American Journal of Hematology, Journal of the American Medical Association, European Journal of Cancer and Clinical Oncology, New England Journal of Medicine, Journal of Laboratory and clinical Medicine and Cancer.

12. Since 1976 I have authored or co-authored several hundred articles which were published in peer reviewed medical and scientific journals. Many of those peer-reviewed publications address HIV/AIDS and related issues. Subjects explored in those publications include: (1) the treatment of HIV/AIDS; (2) the use of HIV/AIDS medications and adverse effects associated

with antiretroviral medications, including AZT (which is in Retrovir and Combivir) and, 3TC (aka Epivir);(3) the pathogenesis, epidemiology and treatment of AIDS-related lymphomas and other cancers; (4) the potential use of AZT in combination with chemotherapeutic agents to treat certain cancers; as well as (5) the pathogenesis and treatment of malignancies in general.

13. I have published over 300 peer-reviewed scientific articles or book chapters. Some of the studies related to HIV/AIDS include: (1) Levine AM, Meyer PR, Begandy MK, Parker JW, Taylor CR, Irwin L, Lukes RJ: Development of B-Cell Lymphoma in Homosexual men: Clinical and Immunologic Findings. *Ann Intern Med* 100:7-13, 1984; (2) Levine AM: Non-Hodgkin's lymphomas and other malignancies in the Acquired Immune Deficiency Syndrome. *Semin Oncol* 14:34-9, 1987; (3) Gill PS, Levine AM; HIV-related malignancy lymphoma: clinical aspects, treatment and pathogenesis. *Ca Invest* 6:413-416, 1988; (4) Levine AM: AIDS-related lymphoma (Review). *Blood* 80:8-20, 1992; (5) Levine AM: AIDS related malignancies: The emerging epidemic (Review). *J National Cancer Institute* 85:1382-97, 1993; (6) Levine AM Lymphoma complicating immunodeficiency disorders. *Ann Oncol* 5(supl 2):S29-35 1994; (7) Levine AM, Bernstein L, Sullivan-Halley J, Shibata D, Bauch-Mahterian S, Nathwani BN: Role of Zidovudine antiretroviral therapy in the pathogenesis of AID-related lymphoma. *Blood* 86:4612-4616, 1995: (8) Gill PS, Mitsuyasu RT, Montgomery T, Huang J, Cabriales S, Testa M, Espina BM, Levine AM, Miles SA: AIDS Clinical Trials Group Study 094: A phase I/II trial of ABV chemotherapy with Zidovudine and recombinant human GM-CSF in AIDS-related Kaposi's sarcoma. *Cancer Journal Scientific American* 3:27-283, 1997; (9) Straus DJ, Huang J, Testa MA, Levine AM, Kaplan LD: Prognostic factors in the treatment of Human Immuodeficiency Virus associated non-Hodgkin's Lymphoma: Analysis of AIDS clinical Trials Group protocol 142- Low dose versus standard-dose m-BACOD plus granulocyte-macrophage colony-stimulating factor. *J Clin Oncol* 16:3601-3606, 1998; (10) Levine AM, Seneviratne L, Espina BM, Wohl AR, Tulpule A, Nathwani BN, Gill PS: Evolving characteristics of AIDS related lymphomas. *Blood* 96:4084-4090, 2000; (11) Ratner L, Lee J, Tang S, Redden D, Hamzeh F, Herndier B, Scadden D, Kaplan L, Ambinder R, Levine AM, Harrington W, Grochow L, Flexner C, Tan B, Straus D: Chemotherapy for Human

Immunodeficiency Virus-Associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. *J Clin Oncol* 19:2171-2178, 2001 (12) Levine AM, Seneviratne L, Espina BM, Wohl AR, Tulpue A, Nathwani BN, Gill PS: Evolving characteristics of AIDS related lymphomas. Blood 96:4084-4090. 2000; and (13) Levine AM, Tulpule, A; Espina, B; Sherrod, A: Boswell, WD; Lieberman, RD; Nathwani, BN: Wells, L: Liposome encapsulated doxorubicin (Myocet) in combination with standard agents (syclosphosphamide, vincrtistine, prednisone) in patients with newly diagnosed AIDS related non-Hodgkin's lymphoma: Results of therapy and correlates of response. J Clin Oncol, 2004: 22: 2662-2670. The complete citations for the above-listed articles and additional peer-reviewed publications are included in my CV, which is attached to this declaration as "Exhibit A".

14. I am very familiar with the history of the AIDS epidemic in the U.S. with respect to the discovery of the HIV virus and the pathogenesis of AIDS generally, as well as the epidemiology and clinical course of the disease. I have been involved in the study, care and treatment of patients with HIV/AIDS and associated malignancies since the earliest recognition of the epidemic, before it had a name. I have personally used Retrovir (AZT), Epivir (3TC), and Combivir (AZT and 3TC) on hundreds of occasions in the treatment of HIV/AIDS patients and in research settings, as well as other antiretroviral medications used to treat HIV infection and associated conditions, and I am familiar with the medical literature concerning these drugs, including potential side effects.

15. I am familiar with the medical literature related to Human Immunodeficiency Virus (HIV) infection and Acquired immunodeficiency Syndrome (AIDS), as well as the diseases associated with those conditions. I have also reviewed the medical records related to the diagnosis and treatment of Robert Zapata.

16. Non-Hodgkin's lymphoma (NHL) is a cancer of the lymphatic system, which is a part of the body's immune system. Although the precise cause of NHL is not fully understood, it has long been appreciated that the disease occurs at greater rates in the setting of chronic

immunosuppression. Indeed, the association between immunosuppression and NHL had been a major focus of research into the disease for a number of years prior to the first report of AIDS.

17. The human immune system protects against infection and other diseases including cancer. As the name implies, HIV attacks the human immune system and thus makes an infected person more susceptible to these diseases. In particular, HIV attacks a type of T-lymphocyte called a CD4 cell, killing it. As the HIV infection progresses, the number of CD4 cells falls. By reducing the number of active CD4 + cells, HIV creates an immunosuppressed condition in the infected person. This immunosuppression caused by a decrease in CD4 cells (and other factors) can lead to infections or the occurrence of malignancies. Some of the malignancies that occur in HIV infected persons appear so often that they are termed "AIDS defining diseases" because they form part of the criteria for a diagnosis of clinical AIDS.

18. Not long after the recognition of AIDS as a new disease entity, and prior to the advent of AZT and other antiretroviral therapies, elevated rates of NHL and another malignancy called Kaposi's sarcoma were reported in the initial surveillance of people diagnosed with this new disease, AIDS. In the early 1980s a person with a significantly depressed CD4+ cell level who contracted Kaposi's sarcoma was defined as having AIDS. As more epidemiologic information was gathered, the association between NHL and AIDS was found to be strong enough that in 1985, the Centers for Disease Control and Prevention (CDC) expanded the definition of AIDS to include certain NHLs among the list of HIV-associated illnesses that constituted the clinical definition of the syndrome known as AIDS. Thus NHL was known to be statistically increased and associated with HIV well before the advent of AZT. In other words, the immune deficiency caused by HIV infection can cause NHL. There are now three recognized AIDS defining malignancies, which include NHL. Kaposi's sarcoma and cervical cancer.

19. HIV is a type of virus called a retrovirus and the medications which kill and inhibit HIV are thus called antiretroviral treatments or therapies. The first compound shown to be effective

against HIV was AZT which came into use in the late 1980s. At that time, various less effective treatments were also being tried. Since the time that AZT was introduced, additional antiretroviral medications have been developed and it is now common practice to use more than one antiretroviral medication concomitantly when treating patients. These highly effective treatments, when used in combination are sometimes referred to as Highly Active Antiretroviral Therapies (HAART). The introduction of AZT followed by other effective antiretroviral medications used in combination radically changed the course of the AIDS epidemic. Before the introduction of these medications, HIV infection was an almost uniformly fatal condition. The antiretroviral drugs changed HIV infection into a treatable chronic disease. However, the antiretroviral treatments cannot kill the HIV completely, and thus are not a cure. Thus, infected persons must continue to take treatments over a lifetime, or the virus and then clinical disease can reemerge.

20. Since the 1980s, the relationship between HIV and NHL, as well as any potential association between AZT and malignancies including NHL, have been extensively studied. As described in the following paragraphs it is now well established that (1) AZT does not cause or contribute to the development of NHL in HIV infected patients, and (2) those persons infected with HIV who experience low CD4+ cell levels are at a greater risk of developing NHL.

21. It is my opinion to a reasonable degree of medical and scientific certainty that neither AZT nor Combivir (which contains AZT) cause NHL. The evidence supporting this opinion is extensive. One manner in which an association or a causative correlation is established in oncology is through epidemiologic studies. There is no epidemiologic evidence that AZT causes NHL or other cancer in patients receiving the medicine. While it was initially suggested in an early study that receipt of AZT might be associated with NHL, a further analysis of that study, as discussed below, does not support such an association. In addition, epidemiologic studies conducted by independent investigators at different university centers have demonstrated there is no association between NHL and AZT. Moreover, epidemiological studies have shown that the use of HAART including Combivir results in a stunning decrease in the occurrence of NHL, not an increase. These studies

also confirm that the major risk factor for contracting NHL among HIV infected patients is low CD4+ cell counts, while AZT confers no increase in risk of NHL.

22. Epidemiological studies on the incidence of AIDS-associated malignancies including NHL continued after the introduction of the first antiretroviral drug (AZT) for AIDS in the mid 1980's. One of the first articles in the medical literature to discuss the NHLs occurring in AZT-treated patients was published by James Pluda, et al. in 1990, "Development of Non-Hodgkin's Lymphoma in a Cohort of Patients with Severe Immunodeficiency Virus (HIV) Infection on Long-Term Antiretroviral Therapy", Annals of Internal Medicine, 113:276-282 (hereinafter the "Pluda Article"). The article reported on a retrospective analysis of medical records of AIDS patients from three studies concerning the use of (1) AZT, or (2) AZT and acyclovir, or (3) AZT and 2', 3'-dideoxycytidine, conducted by the National Cancer Institute between 1985 and 1987. These patients were among the first to receive AZT in clinical trials, and were all severely immunosuppressed with long standing, previously untreated HIV infection and AIDS.

23. Pluda et al. observed that in the cohort (group) studied, those patients who survived for up to three years had a higher than expected rate of NHL. The authors concluded that this increased rate was most likely the result of prolonged survival in the setting of severe immunodeficiency caused by preexisting HIV and AIDS. The prolonged survival was a result of treatment with effective antiretroviral therapy (AZT). The authors also noted that a "direct role of [AZT] therapy itself cannot be totally discounted", although a number of good reasons were given as to why this was most likely not the case.

24. The Pluda Article did not indicate that AZT was the cause of the elevated NHL rates observed in the cohort, nor do the data from the study support such a conclusion. At best, the study generated a series of hypotheses concerning the cause of the elevated NHL rates in this particular, small group of severely immuno-compromised patients. I am aware of Dr. Pluda's conclusions as to the objectives and findings of the study. I agree with him that the Pluda Article does not provide the

kind of data upon which a reasonable oncologist, epidemiologist or other scientist would form an opinion with respect to a purported association between AZT and NHL. Furthermore, the authors themselves made no such claim.

25. There are various reasons why the Pluda Article cannot be used to address whether there is an association between AZT and NHL. First, the Pluda analysis was not a controlled epidemiological study, meaning that there was no systematic comparison between patients who took AZT and those who took no medication, related to the risk of NHL over time. Accordingly, the study, by its very nature, was limited to an analysis of outcomes within the limited study population and cannot be extrapolated to other patient populations without further investigation.

26. Second, Pluda noted that the types of NHL seen in his cohort were of the same types of NHL that typically develop in the setting of HIV infection without AZT therapy. Such findings mitigated against a possible causal relationship between AZT and NHL.

27. Third, the data from the follow-up study on these patients did not find an association between AZT and NHL. When following cohorts, it is important to continue to observe surviving patients even beyond the conclusion of the original study. In fact, the NCI did continue to follow this cohort, as well as additional patients, for up to four and a half years after initiation of antiretroviral therapy. In 1991, NCI reported through the Centers for Disease Control that "[b]ased on available data, the use of AZT is not considered to directly increase the risk for HIV-associated NHL". MMWR, (1991); 40:591,597-600.

28. Even if one were to assume that the data in the Pluda article supported the hypothesis that AZT causes NHL, the study would have absolutely no application or validity from a statistical standpoint to any patients other than those described in the cohort, all of whom were severely immunosuppressed with AIDS or advanced HIV infection. The study would have no statistical

relevance to HIV infected patients on chronic anti-retroviral therapy, and proves no "cause and effect" relationship between use of AZT and development of lymphoma.

29. While the Pluda Article hypothesized, at best, a possible relationship between AZT and NHL, subsequent studies have proven that AZT does not cause NHL. Since the Pluda Article was published, there have been three controlled epidemiologic studies that were designed, in whole or in part, to investigate the role of AZT in the development of NHL. These are (1) Moore, et al., "Non-Hodgkin's Lymphoma in Patients with Advanced HIV Infection Treated with Zidovudine [AZT]", *JAMA* 265:2208-2211, 1991 (Moore Study); (2) Levine, et al., "Role of Zidovudine Antiretroviral Therapy in the Pathogeneis of AIDS-Related Lymphoma", *Blood* 12:4612-4616 (1995) (Levine Study); and (3) Grulich et al, AIDS, 14:133-140, 2000.(Grulich Study) None of these studies showed a causal association between AZT and NHL. Instead, all of the studies confirmed the initial hypothesis of Pluda and his colleagues that the increased rates of NHL among AIDS patients was likely a function of prolonged survival in the setting of profound HIV-induced immunosuppression.

30. The Moore Study was conducted by investigators at John Hopkins University School of Medicine in conjunction with researchers in Chicago and at the University of California, San Diego. This was a 2-year prospective observational multisite analysis of data from 1030 patients who had either AIDS or ARC (advanced AIDS Related Complex) at the time they began treatment with AZT. The investigators then evaluated the incidences of various diseases and infections in this cohort. They found that the incidence of NHL among persons receiving AZT in their study was no different from the incidence of NHL in persons who did not receive antiretroviral therapy, as reported in previous studies. Thus, AZT was shown not to be a factor associated with NHL. Rather, the factors associated with NHL were Kaposi's sarcoma, infection with herpes simplex virus and lower mean neutrophil count.

31. I was the lead author of the Levine Study. In that study we evaluated the incidence of lymphomas in homosexual and bisexual men by conducting a population-based case-controlled study of HIV infected persons. We matched 112 HIV-infected men with lymphoma with 112 HIV infected men who did not have NHL, and had no symptoms or other illness related to HIV. We also matched 49 of the lymphoma cases against 49 additional controls who had AIDS, but not lymphoma. This large carefully controlled study showed no statistical relationship between prior use of AZT or duration of AZT use and the subsequent development of lymphoma. Levine, et al., *supra*, at 4615. Thus, we concluded "that zidovudine [AZT] is not associated with an increased risk of development of lymphoma among HIV-infected homosexual or bisexual men." Levine, et al., *supra*, at 4612.

32. The Grulich Study sought to identify the risk factors for NHL in persons with HIV infection. In this study, 219 HIV infected persons with NHL were compared to 219 HIV infected persons without NHL. This research was conducted by the National Centre in HIV Epidemiology and Clinical Research in Australia, which is a similar institution to the National Institutes of Health (NIH) in the United States. An evaluation of various factors including use of antiviral treatments, history of sexually transmitted diseases, opportunistic infections, and duration of immunodeficiency was conducted. The study found that factors that were not related to NHL included use of nucleoside analogue antiretroviral agents such as AZT. The factor most likely associated with an increased risk of NHL were markers of immunodeficiency such as lower CD4+ counts and a longer period of being infected with HIV. Importantly, in this study, there was actually a reduction in the incidence of NHL among those patients who took combinations of the nucleoside analogues.

33. It is my opinion, and it has been well appreciated by the HIV/AIDS clinical and scientific research communities for many years, that AZT does not cause or contribute to the development of NHL. Indeed, the advent of effective antiretroviral therapies (often containing AZT in addition to other drugs), especially when used early in the treatment of HIV infection, has been associated with a significant decrease in the rates of NHL and other AIDS-related diseases. This has

been repeatedly confirmed by large and well run epidemiological studies of HIV positive persons receiving HAART.

34. In 2004 the CASCADE Collaboration published an assessment of the risks of NHL in 7103 HIV positive patients. See, CASCADE Collaboration, Systemic non-Hodgkin lymphoma in individuals with known dates of HIV seroconversion: incidence and predictors, *AIDS,* 18:673-681 (2004) (Cascade Study). The CASCADE Collaboration is a network of investigators in 13 leading HIV research institutions in European countries, Canada and Australia and includes 26 cohorts of patients, who have well established dates of seroconversion (i.e. dates when they became HIV positive). The participating institutions include governmental health organizations in the UK, Australia, Spain and France. Some of those institutions are the Health Protection Agency (UK), the Institute National de la Santé et de la Recherché Médicale (France), Municipal Health Service (Netherlands), Basel Institute for Clinical Epidemiology and Biostatistics (Switzerland), Medical Research Council (UK), and Instituto Superiore di Sanitá (Italy). The researchers confirmed that the primary risk factor associated with development of NHL is the extent of immunosuppression, as measured by the number of CD4 cells (i.e. low CD4 counts). The study also demonstrated that the incidence of NHL had been decreasing significantly over time as people with HIV received these antiretroviral therapies.

35. Since the beginning of the AIDS epidemic, 49% of the patients with an HIV infection and 69% of the people with full blown AIDS in Switzerland have been enrolled in a continuing study called the Swiss HIV Cohort Study (SHCS). This study has been enrolling people infected with HIV over 16 years of age since 1988 and has some retrospective enrollment going back to 1984. Most of the study participants were enrolled in the study at the time they were first identified as HIV positive. In 2008, investigators published the results of studying 12,959 HIV infected persons in the Swiss Cohort over the years 1984 to 2006. See, Polesel, J., et al, Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *AIDS.* 22:301-306. They confirmed again that low CD4 cell counts were a risk factor in

developing NHL, but found that the use of HAART upon diagnosis could correct for those lower CD4 cell in most patients. Thus, not only were the antiretroviral medicines not associated with NHL but they were actually associated with a stunning decrease in the incidence of NHL in those HIV infected people who were at the highest risk of getting NHL.

36. A very recent study that further confirms these results on the risks of NHL in HIV infected persons is by Engels, E. A., et al, Immunologic and Virologic Predictors of AIDS-Related Non-Hodgkin Lymphoma in the Highly Active Antiretroviral Therapy Era, *J Acquir Immune Defic Syndr,* 54:78-84 (2010) (Engels Study) . This was a retrospective cohort study of 3025 HIV infected persons who received antiretroviral treatment from 1989 to 2006. The investigators found the incidence of NHL was statistically increased when the CD4 cell counts were between 100 to 249 cells per ml, with an even greater risk of NHL when the CD4 count fell below 100. The other statistically significant risk factor for NHL was an HIV viral load of more than 100,000 copies of the virus DNA per ml. The study unequivocally demonstrated that the incidence of NHL fell significantly with the use of HAART (which may contain AZT). Id. At page 81, Figure 1.

37. It is also known that an HIV infected person should continuously take their HAART medications and that interruption in taking these medications can increase the risk of NHL. See, Silverberg M J., et al., Risk of cancers during interrupted antiretroviral therapy in the SMART study, *AIDS,* 21:1957-1963 (2207). This effect occurs because the level of CD4 cells (which provide protection against infection and NHL) decrease as the HIV levels increase after discontinuation of the antiretroviral medications.

38. Among the materials I have reviewed are the medical records relating to Robert Zapata, the death certificate prepared at the time of his death and the autopsy report prepared by Dr. Venus Azar. The following is evident from the medical information concerning Mr. Zapata : (1) He was infected with HIV; (2) At the time Mr. Zapata's HIV infection was first discovered in 2000, he was already immunocompromised as evidenced by his low CD4 counts (CD4 164); (3) His treatment

with antiretroviral medications was successful in lowering his viral load (i.e. the amount of HIV in his system), and raising the number of CD4 cells; (4) At various points Mr. Zapata stopped taking his HIV medications which then caused his viral load to increase and his CD4 counts to drop; (5) He was successfully treated for NHL in 2005-2006 and there is no indication that the NHL ever recurred and no evidence that he had NHL at the time of his death in October 2008, as shown by autopsy; (6) The records indicate that Mr. Zapata was not taking his HAART medications in 2008 prior to his death, and this is consistent with his very low CD4 counts and high HIV viral load in October 2008; (7) Mr. Zapata died of a massive fungal infection with complications related to this infection as the fungus resulted in organ failure and death; (8) NHL was not present anywhere in Mr. Zapata's body at the time of autopsy, and did not in any way contribute to his death; (9) Neither the chemotherapy he received years earlier nor osteonecrosis nor bone marrow necrosis caused or contributed to his death; (10) AZT did not cause or contribute to the development of Mr. Zapata's NHL and AZT did not cause or contribute to his death.

39. Mr. Zapata's diagnosis of HIV infection was supported by appropriate diagnostic tests and confirmed by his clinical course and response to treatment. Diagnoses of HIV infection involve the performing of tests that confirm the presence of the HIV virus. A person infected with HIV will produce antibodies to that virus. Thus one way to determine if a person has an HIV infection is to test for the antibodies to HIV. Such HIV antibody testing was performed on Mr. Zapata on three separate occasions (April 25, 2000, August 19, 2003, and July 12, 2008). There are two basic types of antibody tests called the HIV ELISA test and the HIV Western Blot test, which is generally used to confirm the ELISA, proving that the antibody is against HIV. Both types of these tests were performed on Mr. Zapata and both confirmed the presence of HIV antibodies.

40. In addition to the antibody tests, the presence of HIV may be directly measured through HIV Viral Load tests which precisely quantify the actual number of viruses present in the blood of an infected person. The viruses are quantified by measuring the number or copies of HIV Viral RNA in a blood sample. Such HIV Viral Load testing was performed on Mr. Zapata on 12

separate occasions (April 25, 2000, May 15, 2000, June 7, 2000, December 15, 2000, June 15, 2001, September 4, 2003, November 20,2003, February 2, 2005, December 9,2005, February 2, 2006, July 12, 2008, and September 18, 2008). There are two types of HIV Viral Load tests which work by different methods. These are the HIV Branched DNA, or b-DNA test and the HIV Polymerase Chain Reaction (PCR) test. These types of viral load tests are standard tests that have been developed not only to detect HIV but other viruses as well, and are also used to characterize human DNA. Both of these types of tests are highly accurate and reliable and are licensed for use in the USA. Both of these tests were performed on Mr. Zapata, and both confirmed that he was infected with the virus. Attached hereto as Exhibit B, are copies of medical records of Mr. Zapata reflecting the HIV Antibody and HIV Viral Load tests.

41. Mr. Zapata's HIV infection was also confirmed by his medical condition and course of disease. When first diagnosed in 2000, he reported experiencing night sweats, a persistent cough, had fatigue for months and hairy leukoplakia on physical exam, which can all be associated with an immune depressed condition brought on by HIV infection. These conditions improved and resolved after receiving antiretroviral medication. Further, HIV kills CD4 cells, and the effectiveness of treatment can thus be followed by observing CD4 cell counts over time. Mr. Zapata's CD4 counts were measured on 9 separate occasions (April 25, 2000, June 7, 2000, June 15, 309, September 4,2003, February 2, 2005, December 9, 2005, February 2, 2006, July 12, 2008, and September 18, 2008). These results indicate that when Mr. Zapata was first diagnosed, his CD4 level was quite low (164 cells/ml) consistent with a long standing HIV infection. He responded well to antiretroviral treatment in 2000 and 2001 and his CD4 levels rose to 309 cells/ml. This indicates that antiretroviral medications were associated with a doubling of Mr. Zapata's CD4 cells. The diagnostic testing and medical course unequivocally demonstrate that Mr. Zapata was infected with HIV.

42. In 2000 when Mr. Zapata was diagnosed with HIV, he had two HIV viral load tests showing (respectively) 147,214 and 169,186 copies/ml of HIV. These are very high and such values have been associated with an increased risk for developing NHL. His CD4 count of 164 cells/ml

would also be a well recognized risk factor for developing NHL. He was prescribed Combivir, which contains zidovudine (aka AZT) and lamivudine; and also Sustiva (aka efavirenz). These are all antiretroviral medications for HIV infection and appeared to bring the infection under control. The last indication in his medical records that he received Combivir was July 16, 2002 when he obtained a 60 day supply of the medicine. From that time until September 4, 2003, there is no indication in the records that he was receiving further antiretroviral medications. On September 4, 2003, Mr. Zapata was examined by Dr. Joseph Marzouk at Alta Bates Hospital, during which time Mr. Zapata reported he had tested negative for HIV and did not report his prior treatment nor report receiving HIV medications. At that time, his HIV viral load was >500,000 copies/ml and his CD4 count was 98 cells/ml. Both of these results place him at significant risk of developing NHL. The next indication in the medical records is that Mr. Zapata was receiving antiretroviral medications is September 25, 2003 when he received a prescription for Sustiva and two new antiretroviral medications Viread and Emtriva. There is no indication in the medical records that he ever received Combivir again.

43. I understand that plaintiffs allege in their complaint that side effects of AZT include weight loss, loss of white blood cells (WBC), loss of red blood cells (RBC) and muscle atrophy. These medical conditions are also commonly seen in HIV infection itself. However, the medical records do not indicate that Mr. Zapata suffered from any of these conditions while he was taking Combivir. For example, his WBC count on April 25, 2000 prior to starting Combivir was normal and remained normal on December 15, 2000, and June 15, 2001 while he was taking the medication. His RBC count was low before he took Combivir and did not change during treatment. Nor did he lose weight or atrophy during his Combivir treatment, and in fact his weight increased from 165 1/2 lbs to 177 lbs from 2000 to 2002.

44. From September 4, 2003 to January 29, 2004, Mr. Zapata filled prescriptions for Sustiva, Emtriva, and Viread. However, there is no record in his medical history of his having received antiretroviral medications from January 29, 2004, until November 3, 2005. In December

2005 he was diagnosed as having NHL. He was treated for his lymphoma by R-CHOP a standard chemotherapy consisting of Rituxan, Cytoxan, Adriamycin, Oncovin, and Prednisone from December 2005 through March 2006. The treatment was associated with a complete disappearance ("complete remission") of his NHL

45. In 2006 Mr. Zapata was prescribed the following HAART medications: Viread, Sustiva, Emtriva, and Truvada. In January and March of 2007 Mr. Zapata filled a prescription for Truvada. It is unclear whether he took his medications. On July 10, 2008, he was seen for back pain and reported that he had not taken his HIV medications since the middle of 2006. Other reports in the records indicate that he had not taken his HIV medications for several years. On July 12, 2008, Mr. Zapata had a viral load of 83,100 copies/ml and a CD4 count of 117 cells/ml indicating he was seriously immunosupressed. Further testing on September 18, 2008, revealed an HIV viral load of 92,932 copies/ml and a CD4 level of 65 cells/ml showing further deterioration in his immune condition. The records reflect that his physicians attempted to restart Mr. Zapata on HAART therapy, but he resisted or refused.

46. In July and August 2008, when Mr. Zapata had unexplained back pain, he underwent extensive testing to determine if his NHL had recurred. These tests included a biopsy of his lymph nodes, CT scan of his thorax, pelvis, and abdomen, MRI of cervical, lumbar and thoracic spine, chest x-rays, bone marrow biopsy with flow cytometry immunophenotyping, and PET/CT scans from the skull to the thighs. Some of these tests were repeated more than once. These tests indicate a thorough and extensive examination for NHL. These tests revealed no evidence that his NHL had recurred. Dr. David Pfister, who was the treating oncologist, concluded that there was no evidence of NHL.

47. On July 15, 2008 a bone marrow report indicated bone marrow necrosis but no involvement of lymphoma was found. There are also references in the medical records to osteonecrosis but there is no diagnostic test or assessment that supports that diagnosis. Bone marrow

necrosis and osteonecrosis are two separate diseases and the bone marrow report does not indicate a diagnosis of osteonecrosis.

48. Treatment for Mr. Zapata's back pain continued in September and October of 2008, during which time he was receiving strong pain killers including Fentanyl and Dilaudid. On October 25, 2008 he was brought to the Alameda Hospital, because of a worsening condition. He reportedly had not eaten or taken water for 3 days and was delusional. Mr. Zapata had oral thrush, a fungal infection for 3 days. It was thought that he had possibly aspirated (breathed in) emesis (vomit) into his lungs. His vital signs and reflexes were poor. An infection was suspected and the plan was to start him on antibiotics. Mr. Zapata died on October 26, 2008. A death certificate of October 26, 2008 listed the causes of death as aspiration pneumonia, upper GI bleeding, disseminated intravascular coagulation and HIV.

49. An autopsy was performed on Mr. Zapata on November 3, 2008 by Dr. Venus Azar. This included both a physical examination of Mr. Zapata's body, as well as microscopic evaluation of tissues. Samples were taken and stained to confirm pathological assessments. It was noted that "all lobes of both lungs focally showed fungal forms filling alveolar spaces with extensive hemorrhagic necrosis". Samples taken also confirmed the extensive fungal infection observed grossly. Dimorphic fungal forms similar to those in the lungs were seen in the esophagus and vocal cords. The kidney and liver both showed inflammatory cell infiltrates. There was apparent macrovesicular steatosis in the liver. There was no evidence of pathologic changes in the adrenal, the lymph nodes, nor any necrosis or neoplastic process (i.e. cancer) in the spleen or elsewhere. Sections of the rib and vertebral bone were specially stained and showed no evidence of neoplastic process or fungus. The examiner concluded that Mr. Zapata died of disseminated fungal infection. In other words, he died of an infection caused by a fungus, that filled all areas of both his lungs, and also invaded the esophagus and vocal cords. This fatal infection was caused by his terribly weakened system due to HIV/AIDS.

50. Specimens were taken at autopsy, were analyzed and demonstrate that Mr. Zapata did not have lymphoma at the time of his death. Rather, the autopsy confirmed that fungal infection was the cause of death, disrupting his ability to breath as well as causing severe metabolic problems which led to his death. Mr. Zapata died from an infection. In the months before his death his CD4 count was reported to be 65 and his viral load was 92,932 copies/ml, which demonstrates that his HIV was uncontrolled and he was severely immunocompromised, making him vulnerable to the fungal infection that killed him. His death was preventable, since his history shows that he responded well to antiretroviral therapies when he took them. His apparent refusal to accept HAART therapy led to the immunosuppressed conditions that led to his overwhelming fungal infection, that led to his death.

51. The medical records confirm that Mr. Zapata did not have NHL at the time that he died and NHL did not contribute to his death. The bone marrow biopsy mentioned in the medical records indicated necrosis, without presence of NHL. There is no evidence that Mr. Zapata had osteonecrosis, and the bone marrow necrosis mentioned in one of his reports was not confirmed at autopsy. Osteonecrosis or bone marrow necrosis neither caused or contributed to his death.

52. I am familiar with the package insert for Combivir. It contains a section on Carcinogenesis, Mutagenesis, and Impairment of Fertility. This section describes animal studies performed by GlaxoSmithKline as well as other scientists and research institutions, including describing the tumors that appeared in some of the animals. The package insert accurately and reasonably presented the information on the carcinogenicity and mutagenicity of the product, based on my knowledge of the medical literature.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Executed this 17th day of DECEMBER, 2010, at Los Angeles, California.

By: _____
Alexandra M. Levine, M.D., MACP