AIDS Medical Background*

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First of all, I would like to thank the Shaare Zedek Medical Center for allowing me to come to Eretz Yisroel and participate in this conference and, of course, to the committee for selecting me. Just to give you the appropriate background, my interests are not primarily as a retrovirologist. My laboratory research interests are related much more to things that I can see under the microscope like fungi and protozoa and especially as to how they interact with human host defense cells. However, originally when I decided to become an infectious disease expert, one of the reasons that I chose this subspecialty is that this is one area in medicine where you can do something for the patient. You can cure the patient. I didn't want to deal with something like oncology, hematology. And then in 1981 a little event happened and my life has never been the same ever since. Before I go any further, I need to apologize to the audience for the following reason. First of all, they gave me 40 minutes to discuss whatever has happened to AIDS since its beginning, an impossible task. Number two, what makes this topic and this particular talk very difficult for me is the range of the audience. In this audience there are, I'm sure, experts at the molecular level all the way to people who have really very little contact with this virus either in the test tube or in the patient, and their understanding of this disease is on the level of the layperson. I will attempt to make at least parts of this talk available to everyone. Thus, those of you who are molecular biologists, cellular biologists and great clinicians, my apologies to you if the material that I'm presenting is already very familiar to you. And to those of you who are perhaps not familiar with the many aspects of AIDS and some of the material is a little bit beyond you, I also ask from you *Mechilah*.

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The Medical information which Prof. Jacob Fleischmann presented in the colloquium was part of the data needed for the halachic decision of Rabbi Y. Neuwirth in his responsa as follows in this book pp. 240-245.

While serological evidence dates AIDS back to the fifties,[1,2] the first five recognized cases were reported by UCLA faculty.[3,4] At the time I was an infectious diseases fellow at UCLA and consulted on one of these patients. He was a perfectly healthy male model commuting between Los Angeles and Paris, sent over to us from Cedars-Sinai Hospital where he presented with pain on swallowing. He was found to have thrush in his mouth, and his barium swallow looked like candida esophagitis. My review of the literature at the time ties this event to Maimonides Hospital. The definitive paper on candida esophagitis at that time was in the Journal of Gastroenterology in 1976, published by Dr. Baruch Kodsi *et al.*[5] from Maimonides Medical Center. The paper pointed out two important things. Candida esophagitis never happens in healthy people, number one. Number two, to prove the diagnosis, you really have to do a biopsy to show invading hyphal elements of the fungus. So I managed to convince my attending at UCLA to do a biopsy on this patient. And lo and behold, the biopsy came back showing no invasive fungal disease but with evidence for cytomegalovirus (CMV) esophagitis. Now we knew that CMV is another pathogen causing significant illness in immunocompromised patients. A couple of weeks later he came back with infiltrates in his lungs, and because of our previous experience we went for a biopsy early and to our astonishment it came back positive for pneumocystis carinii (PCP). We used to see at UCLA prior to AIDS about 5 or 6 cases of PCP per year in our leukemics, but not in apparent normal hosts. At that moment, I said to my attending, I don't know what's going on with this person, but something is wrong with his immune system. Well, a little bit of a history.

Though the initial cases reported were from UCLA, we do have serological data going back at least into the 50's in Africa. That it was not recognized is not surprising since there are many

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1. Poit P., *et al*: AIDS: An interbational perspective. Science 239:224, 1987
2. Berkeman R.L., *et al*: Epidemiology of human immunodeficiency virus infection andacquired immunodeficiency syndrome. *Am J Med* 85:761, 1989
3. Centers for Disease Control: *Pneumocystis* pneumonua – Los Angeles. *M.M.W.R.,* 30:250-252, 1981
4. Gottlieb, M. S., *et al*: *Pneumocystis* carinii pneumonua and Mucosal candidiases in previously healthy homosexual men. *N. Engl. Med,*. 305:1425-1431, 1981
5. Kobsi B. E., *et al*, Candida esophagitis: a prospective study of 27 cases. Gastroenterology, 71:715, 1976

wasting diseases on that continent. For example, a disease known for many years as "slim disease" in Africa, is now known to be caused by HIV. In the United States it didn't take us more than a few months to realize that we were dealing with something very new. Table 1 lists some of the historical highlights related to this disease. Among the more mysterious cases is the 14 year old in St. Louis, without travel or risk factors, who died in 1968. One can also see the exploding nature of this epidemic. It took from 1981 to 1985 to diagnose the first 10,000 cases in the US.[6]

Table 1 – **Brief History of HIV**

1959 -	Retrospective study of sera positive for HIV in Africa
1968 -	A 14 year old male dies in St. Louis, USA, studies of his frozen tissues find HIV
1981 -	First cases officially reported by UCLA faculty
1982 -	First 1000 cases reported in US
1983 -	Etiologic virus discovered, later named HIV
1985 -	First 10,000 cases reported in US Serological test becomes available
1986 -	AZT found to be beneficial
1989 -	First 100,000 cases reported in US
1991 -	First 100,000 deaths reported in US
	First 200,000 cases reported in US
1992 -	Low CD4 cell counts without HIV reported
	First 250,000 cases reported in US
	First 170,000 deaths reported in US

Over the next four years we reached 100,000.[7] It took only two years to double this number.[8] Table 2 shows the current estimates

Table 2 – **Estimated number of HIV cases by region as of mid – 1993**

Western Europe	500,000
Eastern Europe and Central Asia	50,000
East Asia and Pacific	>25,000
South and Southeast Asia	>1,500,000
Australia	>25,000
North Africa and Middle East	>75,000
Sub-Saharan Africa	>8,000,000
North America	>1,000,000
Latin America and the Caribbean	1,500,000

6. Castro K. G., *et al*: The Acquired immunodeficiency syndrome: Epidemiology and risk factors for transmission. Medical Clinics of North Amrica 70:635, 1986
7. Castro K. G., *et al*: The acquired immunodeficiency syndrome: Epidemiology and risk factors for transmission. Medical Clinics of North America 70:635, 1986
8. First 100,000 cases of acquired immunodeficiency syndrome – United States. *M.M.W.R.* 38:561, 1989

of HIV infections worldwide as of mid 1993.[9] It is clearly a worldwide epidemic with sub-Saharan Africa being the most devastated area. I understand there are about 200 cases so far here in Israel.

Table 3 – **Transmission of HIV**

Parenteral
Transfusion of blood and its products
Needle sharing by drug users
Needle stick, wound and mucous membrane exposure in healthcare
Sexual
Male to male
Male to female
Female to male
Perinatal
Intrauterine
Peripartum
Post partum (breast feeding)

A decade of experience with this disease has established the modes of transmission of HIV and these are listed in Table 3.[10] For adults the two main routes are parenteral and sexual pointing out the importance of human behavior in the spread of this disease. Even perinatal spread is tied to behavior as the great majority of children infected are born to HIV infected mothers who are drug users. Casual and even close personal (but not sexual) contacts such as exists in the household, workplace or school, are not a risk for transmission. Insects have been investigated as potential vectors and to this date there is no evidence that they are.[11] Breast feeding during the post-partum period can transmit HIV[12] indicating that oral or gastrointestinal mucosa may be a portal of entry for the virus. This has *halachic* implications for a *Mohel* who has to do *metzitza*. A variety of unusual transmissions have been reported. Some, like organ transplantation[13] and artificial insemination[14] are

9. Centers for Disease Control: The second 100,000 cases of acquired immunodeficiency syndrome – United States, June 1981 – December 1991. *M.M.W.R* 41:28, 1992
10. Merson M. H., Slowing the spread of HIV: Agenda for the 1990's. *Science* 260:1266
11. Jaffe H. W., *et al:* Acquisition and transmission of HIV: Infectious Disease Clinics of North America, 2:299, 1988
12. Webb P. A., *et al:* Potential for insect transmission of HIV: experimental exposure of *Cimex hemipterus* and *Toxorhynchites amboinensis* to human immunodeficiency virus. *J infect Dis* 160:970, 1989
13. Oxtoby M. J.: Human immunodeficiency virus and other viruses in human milk: Placing the issue in broader perspective. *Pediatr Infect Dis J* 7:825, 1988
14. Centers for Disease Control: Human immunodeficiency virus infection transmitted from an organ donor screened for HIV antibody – North Carolina. *M.M.W.R.* 35:306, 1985

predictable. Transmission via oral sex has occurred[15] again pointing to the oral mucosa as a portal of infection. Female to female transmission has been reported but is rare.[16] Infection through a bite is not surprising as exchange of blood is likely to occur.[17] One report of a wife becoming infected after kissing an impotent HIV positive husband[18] turned out to be incorrect.[19] The well known case of an HIV positive dentist in Florida infecting several of his patients needs a comment.[20] The CDC has traced his patient's isolates to him using DNA sequencing analysis. Assuming that this is correct, we need to consider that neither before nor since has there been a case of a dentist infecting a patient. When an extremely rare event occurs with the same source several times clearly something unusual had to happen. We do not know what this was. There is one group referred to by the CDC as having no identifiable risk (NIR).[10] Those of us dealing with this disease are aware of the difficulty in obtaining accurate histories of risk factors, but the most puzzling among this group are the pediatric cases.

The distribution of risk factors varies geographically.[9] In the US and Europe it is still predominantly homosexual activity and intravenous drug use. In the US though the fastest growing group may be the heterosexuals, especially teenagers. In Africa it is predominantly a heterosexual disease. This may be partly due to associated sexually transmitted diseases which cause breakdown of the mucosa enhancing viral transmission.[10] Other factors postulated have been cervical ectopia and intercourse during menstruation. Risks associated with specific activities are not easy to quantify. Table 4 lists the USA and European experience.[10,21] Recently there has been a tendency in the lay press to play down

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15. Stewart G. J., *et al*: Transmission of human T-cell lymphotropic virus type III (HTLV-III) by artificial insemination by donor. *Lancet* 2:581, 1985
16. Mayer K.H., *et al*: Human immunodeficiency virus and oral intercourse. (Letter.) *Ann Intern Med* 107:428, 1987
17. Marmor M, *et al:* Possible female-to-female transmission of human immunodeficiency virus. (Letter.) *Ann Intern Med* 105:969, 1986
18. Wahn V, *et al*: Horizontal transmission of HIV infection between two siblings. *Lancet* 2:694, 1984
19. Salahuddin S. Z., *et al*: HTLV-III symptom-free seronegative persons. *Lancet* 2:1418, 1984
20. Groopman J. E., Personal communication Centers for disease control: Update: transmission of HIV infection by invasive dental procedures – Florida. *M.M.W.R* 40:377, 1991
21. Rubin R. H., Acquired immunodeficiency syndrome, in Scientific American Medicine, sect. 7 chapter XI, 1993

the risk of female to male transmission. While it is clearly less than male to female, nonetheless it is real. Blood, when properly processed is quite safe, though the risk is not yet zero.

Table 4 – **Transmission Risks (USA & Europe)**

Male to female:	10 - 20%
Female to male:	1 - 12%
Perinatal:	13 - 33%
Healthcare worker needle exposure:	3 - 5 per 1000 episodes
Transfusion:	1 in 40,000 - 150,000 or less

Table 5 summarizes the African experience.[22] HIV-2 is seen primarily in Africa and in those who have traveled there. The blood supply is still seriously tainted on that continent. One fact which might be interesting to this audience is that circumcision seems to decrease the rate of transmission but by no means is it 100% protective.[23]

Table 5 – **AIDS in Africa**

HIV-1 and HIV-2
Heterosexual transmission 80% (of total)
Perinatal transmission 10% (of total)
Blood transfusion 10% (of total)

Table 6 – **Isolation of HIV from body fluids and cells**

Plasma
Peripheral mononuclear cells
Bronchial fluid
Tears
Ear secretions
Saliva
Urine
Vaginal and cervical secretions
Semen
Milk
Cerebrospinal fluid

Table 6 lists the bodily fluids from which HIV has been isolated. The virus might be free in fluid or within lymphocytes. Experience has shown us that the mere presence of the virus in a fluid does not make it a vehicle for transmission. For example, as we have already mentioned routine kissing is not a risk but the CDC does recommend against kissing with high negative pressure in the oral cavity which

22. O'brien T. R., *et al:* Acquisition and transmission of HIV, in The medical management of AIDS, 3rd ed. Sande M. A. and voberding P. A. eds. W. B. Saunders Co. p. 3-17, 1992
23. Cameron D. W., *et al*: Female-to-female transmission of human immunodeficiency virus type 1: Risk factors for sroconversion in men. *Lancet* 2:403, 1989

might lead to bleeding.[24]

The incubation period for the development of AIDS varies with age.[21] Children infected by transfusion before the age of five have an incubation period of less than two years. Adults have an incubation period from eight to ten years. When looking at the distribution of disease by age, one sees the truly devastating aspect of this disease as it primarily hits young adults. Recently, the press has focused on long term infected individuals who have not developed AIDS. The actual data is as follows; so far about 60% of infected individuals have developed AIDS.[9] Furthermore, mathematical models are predicting that close to 100% eventually will.[25] Thus long-term survivors, and now some of them are going beyond 12 years, probably represent just the edge of the bell-shaped curve. Clearly this retrovirus does not behave like HTLV-1 where only perhaps 10% of the people who are infected will come down with leukemia or the other manifestations of that virus.[26]

Now about the virus itself. We probably have accumulated more information about HIV than any other human viral pathogen. I will highlight only the main features.[27] Similar to other retroviruses it has within a host derived lipid bilayer, core proteins surrounding the genomic RNA. Protruding through the lipid bilayer are rod and sphere shaped envelope proteins. Working our way from the core to the surface we first encounter two identical genomic RNAs making this virus diploid. With them are two enzymes necessary for replication and integration, namely reverse transcriptase (RT) and integrase. Surrounding them is the core protein of which p24 is the major component and just inside the lipid bilayer is the matrix containing p17. Protruding through the bilayer are glycoproteins gp120 and gp41. At the genomic level it has the standard retroviral structural genes: *gag* which encodes the proteins that form the virion core; *pol* which encodes for reverse transcriptase integrase and protease; *env* which encodes the envelope glycoproteins. In addition it has several overlapping open

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24. Wofsy C. B., Prevention of HIV transmission. Infectious disease clinics of North America. 2:307, 1988
25. Lifson A. R., *et al*: Progression and clinical outcome of infection due to human immunodeficiency virus. *Clin Infect Dis* 14:966, 1992
26. Rosenblatt J. D., *et al*: Infection with HTLV-I and HTLV-II: evolving concepts. *Semin Hematol* 25:230, 1988
27. Feinberg M. B., Slow virus infections and retrovirus infections, in *Scientific American Medicine*, sect 7 Chapter XXXII, 1989

reading frames containing several regulatory and accessory genes. These include *tat, rev, nef, vif, vpr,* and *vpu* for HIV-1 and *vpx* for HIV-2. Deletion analysis has given us some insight into the function of these genes but we have a long way to go in fully understanding their activities. *Tat* and *rev* are essential for the optimal transcription and translation of structural gene products. *Nef* appears to maintain latent infection. *Vif* appears to be necessary for infectivity and *Vpu* for the release of budding virions from the surface of infected cells. Flanking these genes are long terminal repeats (LTRs) which contain regulatory elements involved in gene expression.

A simplified version of the life cycle of HIV is as follows:[28] the virus via its GP120 molecule attaches itself to a CD4 receptors on cells. GP41 facilitates entry of the virus into the cell by fusing with the target cell membrane. There is some data which suggest that the virus might gain entry into the cell via other routes: for example, being part of a antigen-antibody complex, and entering cells via Fc receptors. There is also data that for some neural and epithelial cells the galactosyl ceramide molecule may function as a receptor. Once endocytosed, the uncoated viral single stranded RNA is transcribed into double stranded DNA (provirus) by reverse transcriptase. It is the infidelity of RT that allows frequent mutations leading to variations in isolates making it more difficult for the immune system to handle this virus. The provirus enters the cell nucleus and integrates into the host genome. This is one of the critical features one needs to contemplate when thinking about cure, as these cells are permanently transformed. Under certain conditions, the provirus is transcribed, giving rise to viral RNA, coding for viral proteins which ultimately get assembled to make complete virions. These progeny are released by budding from the cell membrane.

Table 7 shows a variety of cells susceptible to HIV infection at least in vitro.[29,9] Some of these, such as fibroblasts appear to lack CD4 receptors again suggesting that the virus can be internalized by other means. What direct effect on cellular and ultimately organ function this has is not fully understood. For example, a number of

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28. Wiess R. A., How does HIV caus AIDS. *Science* 260:1273, 1993
29. Levy J. A., Viral and immunologic factors in HIV infection, in The Medical Management of AIDS, 3rd ed. Sande M. A. and Volberding P. A. eds. W. B. Saunders Co. p. 18-32, 1992

Table 7 – **Cells susceptible for HIV**

T and B Lymphocytes	Bowel epithelium
Macrophages	Renal epithelium
Promyelocytes	Langerhans cells
Dendritic cells	Fibroblasts
Astrocytes	Enterochromaffin cells
Oligodendrocytes	Cervical cells
Capillary endothelium	Megakaryocytes
Cardiac myocytes	Trophoblastic cells

papers have been published looking at macrophage function after in vitro HIV infection and the results are conflicting. Overall, macrophage function, at least as studied in vitro, does not seem to be severely impaired. In vivo these cells have been suspected as reservoirs for viral replication and dissemination. A variety of functional abnormalities have been reported for other cells of the immune system from HIV infected individuals. B lymphocytes are generally activated leading to hypergammaglobulinemia, circulating antigen-immune complexes and autoantibodies. These patients also respond poorly to vaccines and have increased incidence of infections with capsular bacteria. Natural killer cells, while not targets for HIV, have decreased surveillance activity.

The pivotal cells involved in immune suppression in HIV are the T-lymphocytes. While a number of qualitative deficiencies have been described for these cells, it is their ultimate depletion that leads to end stage disease. These deficiencies include impaired expression IL-2 receptors, decreased IL-2 and interferon-gamma production[38] and impaired helper function for B-lymphocytes to produce immunoglobulin. Table 8 lists possible mechanisms which either destroy or disarm T-lymphocytes.[28] Some destroy the cells directly, such as lysis and syncytia formation. A more controlled destruction involves apoptosis which represents genetically

Table 8 – **Possible mechanisms of lymphocyte impairment by HIV**

Direct Cytopathy	
	Lysis
	Syncytia formation
Indirect Mechanisms	
	Apoptosis
	Autoimmune
	Superantigen
Cofactors	
	CMV, mycoplasma, EBV, etc.

programmed death of cells.[30] As part of normal physiology, this process eliminates T-lymphocytes capable of recognizing self-antigens. There is in-vitro evidence that the interaction of GP-120 with the CD4 receptor can trigger this process. Another mechanism postulated is autoimmunity. Since MHC class II products share some homology with GP-120 and GP-41 proteins, autoantibodies might be generated by HIV infection reacting with T-lymphocytes. Finally, some antigens can interact with a less specific portion of the beta chain of the T-cell receptor leading to anergy or deletion of a large number of T-lymphocytes. Such antigens are referred to as *superantigens*, and there is some data suggesting their presence in HIV infected patients. Finally, coinfection with other viruses like CMV or EBV may play a role in immune destruction. Recently a mycoplasma has been touted for such a role, but none of this is proven.

What happens to these patients clinically? Studies on patients diagnosed with their initial infection[31] show significant plasma viremia which declines to almost undetectable levels after the appearance of HIV antibodies. This period has been referred to as latency.

As full blown AIDS develops and CD4 positive T-lymphocytes decline, the virus reappears and increases as the patient dies. P-24 antigens shows the same pattern. The latent period during which only a small fraction of the circulating T-lymphocytes are found to be HIV infected has been puzzling. Recent data, however, has begun to elucidate what really happens.[32,33] Investigators using quantitative PCR and in-situ hybridization techniques have shown that active multiplication of HIV and systematic infection of T-lymphocytes continues in lymph nodes. The cell that plays a central role in this process is the follicular dendritic cell (FDC) which traps and presents HIV to T-lymphocytes. Ultimately, these cells die and on electron microscopy one can see the destruction of the architecture of the lymph nodes leading to a decrease of CD4+ cells. With the increasing viral burden, spillover into the circu-

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30. Gougeon M. L., *et al*: apoptosis in AIDS, *Science* 260:1269, 1993
31. Daar E. S., *et al:* Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. *N Engl J Med* 324:961, 1992
32. Embrtson J, *et al*: Massive covert infection of helper T-lymphocytes and macrophages by HIV during the incubation period of AIDS. *Nature* 362:359, 1993
33. Pantaleo G, *et al*: HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. *Nature* 363: 355, 1993

latory system occurs leading to increasing viremia. It is at this point when the patient becomes the target of a number of opportunistic infections.

Thus, while there may be a clinical latency, microbiologically the process is ongoing and unrelenting.

The case definition of AIDS has been expanded by the CDC to include patients with CD4+ T-lymphocyte count of less than 200/mm^3.[34] Also added were pulmonary tuberculosis, recurrent bacterial pneumonia, and invasive cervical carcinoma. The previous criteria otherwise remains the same. The clinical classification system developed by the CDC is based on a combination of CD4+ T cell count and clinical categories using a numerical and alphabetical combination. CD4+ T cell counts of $\geq$500/mm^3=1; 200-499/mm^3=2; 200/mm^3=3. Asymptomatic, persistent generalized lymphadenopathy, acute HIV infection are in category A; symptomatic but not AIDS in category B; and AIDS is category C. This classification system allows us to compare efficacy of clinical trials.

Table 9 – **Testing for HIV infection**

Viral Culture
Antibody tests
Elisa
Western Blot
Radioimmunoprecipitation
Indirect immunofluorescence
p24 antigen
PCR

Table 9 lists the tests available to detect HIV infection.[35] The primary way we diagnose this disease is by looking for antibodies. The ELISA test is most commonly used today, and has a specificity and sensitivity close to 99%. Each positive ELISA is still confirmed with a Western Blot. Viral cultures which can be done quantitatively are tedious and they are mostly used in research laboratories. The p24 antigen assay is only useful in early or late infection and is not useful as a screening test. PCR, when done carefully, can detect very low viral loads within hours, but false amplifications can lead to unnecessary anxiety. It is commercially available, but one needs to know the quality of the laboratory doing it.

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34. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *M.M.W.R* 41:961, 1992
35. Saag M. S., AIDS Testing; Now and in the future, in *The Medical Management of AIDS*, 3rd ed. Sande M. A. and voberding P. A eds. W. B. Saunders Co. P. 33-35, 1992

A variety of prognostic markers have been described in the literature, including neopterin, and beta2 microglobulin.[36] Clinically, our most useful marker is the CD4+ T cell count. Table 10 lists the complications related to declining CD4+ T cell counts. In addition to knocking out the immune system, HIV can cause complications with many other systems. Time does not permit me a detailed description and I will highlight only a few.[21] The most common skin manifestations are seborrheic dermatitis and acne-like lesions. Oral manifestations include thrush and hairy leukoplakia.

Table 10 – **CD4+ T cell counts & complications**

500-250:	Candidiais, Tuberculosis
200-150:	KS, PCP, lymphoma, cryptosporidia
125-75:	MAI, HSV, toxoplasmosis, cryptococcosis, esophageal candida
50:	CMV retinitis

Neurologically we most commonly see AIDS dementia and peripheral neuropathies. Intractable diarrhea from a variety of causes can be devastating to these patients. Hematologically, almost any cell line in the bone marrow can be suppressed. Idiopathic thrombocytopenic purpura is not unusual and will frequently respond to high dose AZT therapy. These patients can develop pericardial effusions which occasionally lead to tamponade. Of the endocrine system, it is the adrenal gland that is most commonly involved with adrenalitis, but clinical adrenal insufficiency is unusual. Focal and segmental glomerulosclerosis (FSGS) of the kidneys frequently leads to end stage renal disease. A variety of disorders might involve the musculoskeletal system and these include arthritis, polymyositis and vasculitis. Malignancies include Kaposi's sarcoma and non-Hodgkin's lymphoma.

You are familiar with a long list of opportunistic infections these patients are susceptible to.[21] I will just highlight a few of the more interesting questions related to infections. While atypical mycobacteria like MAI cannot be treated, and most fungal infections require lifelong therapy, why is it that tuberculosis can be successfully treated? Incidentally, a most serious complication is the development of multiple drug resistant tuberculosis among

36. Clement M., *et al*: Natural history and management of the seropositive patient, in *The Medical Management of AIDS*, 3rd ed. Sande M. A. and Volberding P. A. eds. W. B. Saunders Co. p. 87-96, 1992

these patients which can potentially infect HIV negative population, too. Why is it that intracellular pathogens like listeria monocytogenes and legionella pneumophila do not have an increased incidence among HIV patients? While one of the most common clinical manifestations of HIV infection is thrush, we see very little invasive candidiasis in these patients.

Table 11 lists our therapeutic approach to these patients.[37] AZT has been shown to delay the onset of AIDS, however it remains controversial if it prolongs survival. Our capacity to keep these patients alive longer is mostly related to our aggressive treatment of such opportunistic infections as PCP and prophylactics against them. Treatment of malignancies remains dismal. Vaccines which have so far been tested on humans have been disappointing.[39] The most promising vaccine so far appears to be one where the *nef* gene has been deleted from SIV and this has been 100% protective against the complete virus in monkeys. Future approaches to therapy include every step of viral-cellular interaction, from initial attachment to release and maturing of virions.[40] As our understanding at the molecular level increases so will likely our therapeutic armament.

Table 11 – **Therapy of HIV Infection**

Antiretroviral
Treatment of opportunistic infections
Prophylaxis of opportunistic infections
Treatment of malignancies

While the overall picture may appear to be bleak, in fact, we have all the knowledge and the technical capacity to stop this epidemic in its tracks. The one variable which we can not control is human behavior. This is an important point to contemplate at a conference on Ethics and Halacha.

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37. Fischl M. A., Treatment of HIV Infection, in *The Medical Management of AIDS*, 3rd ed. Sande M. A. and volberding P. A. eds. W. B. Saunder Co. p. 97-110, 1992
38. Murray H. W. *et al*: Imapaired production of lymphokiness and immune (gamma) interferon in the acquired immunodeficiency syndrome. *N Engl J Med* 310:883, 1984
39. Salk J., *et al*: A strategy for prophylactic vaccenation against HIV. *Science* 260:1270, 1993
40. Johnston M. I., *et al*: Present status and future prospects for HIV therapy. *Science* 260:1286, 1993