Aspects of Solid Organ Transplantation in HIV-Infected Patients

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June 25, 2010

This is to acknowledge that Dr. Wada has disclosed no financial interests or other relationships with commercial concerns related directly to her program. Dr. Wada will be discussing off-label uses in her presentation.

INTRODUCTION:

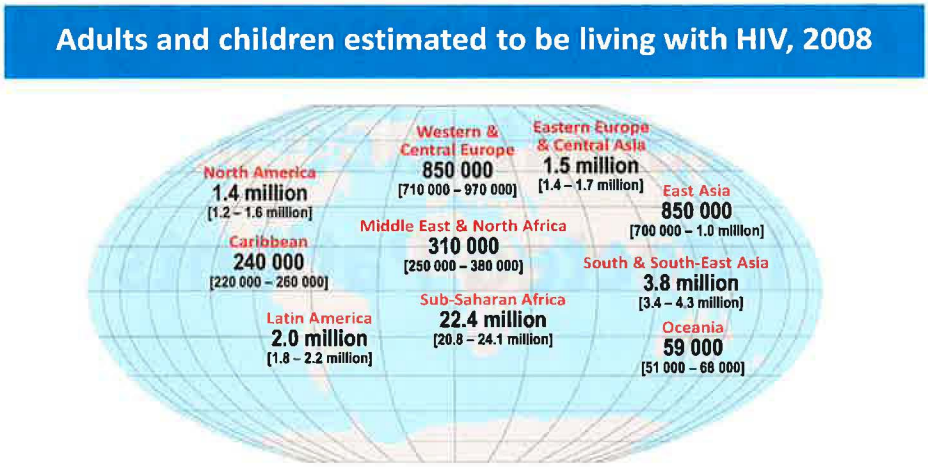


Figure 1 (2)

In 1981, the first cases of AIDS (Acquired Immunodeficiency Syndrome) were reported to the Centers of Disease Control and Prevention (CDC).(1) More than 25 years after the first reports of AIDS, more than 1 million cases of AIDS have been reported in the United States. (1) In 2009, the World Health Organization reported 22.4 million people living with HIV (Human Immunodeficiency Virus) in the Sub-Saharan Africa and 3.8 million people living with HIV in South and South-East Asia. (2) Sub Saharan Africa is the region most affected and is home to 67% of all people living with HIV worldwide. (2) In 2009, the World Health Organization reported 1.4 million people living with HIV in North America. (2) Though, in the United States, and even more so in Africa and Asia, the human toll has been substantial, in the last 25 years, there have been major advances in HIV testing, prevention and treatment. Not only is there a cornucopia of HIV medications to control the HIV virus, but we have advanced so much in our abilities to diagnose and treat the myriad of HIV associated opportunistic infections and malignancies that plague our HIV-infected patients.

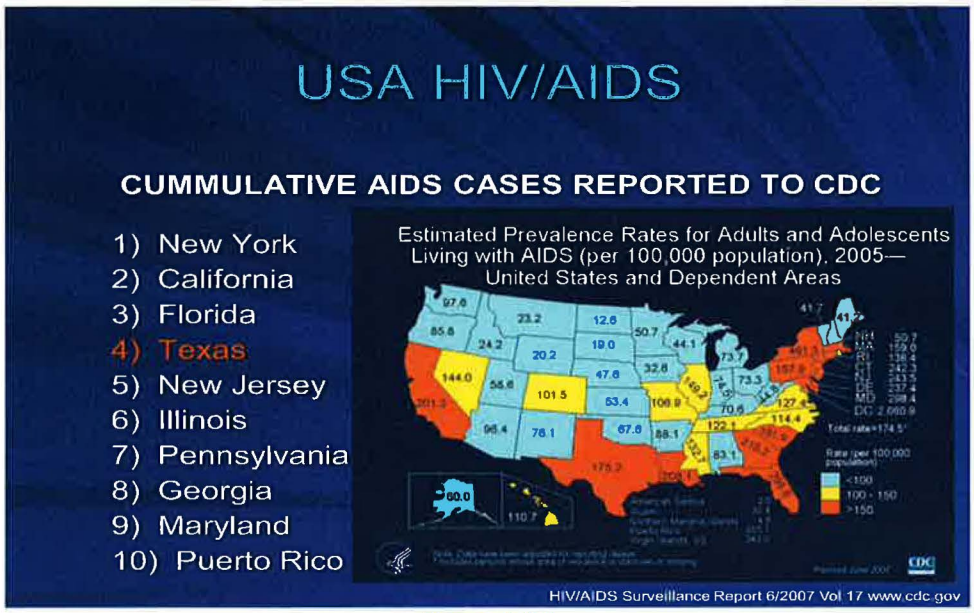


Figure 2 (3)

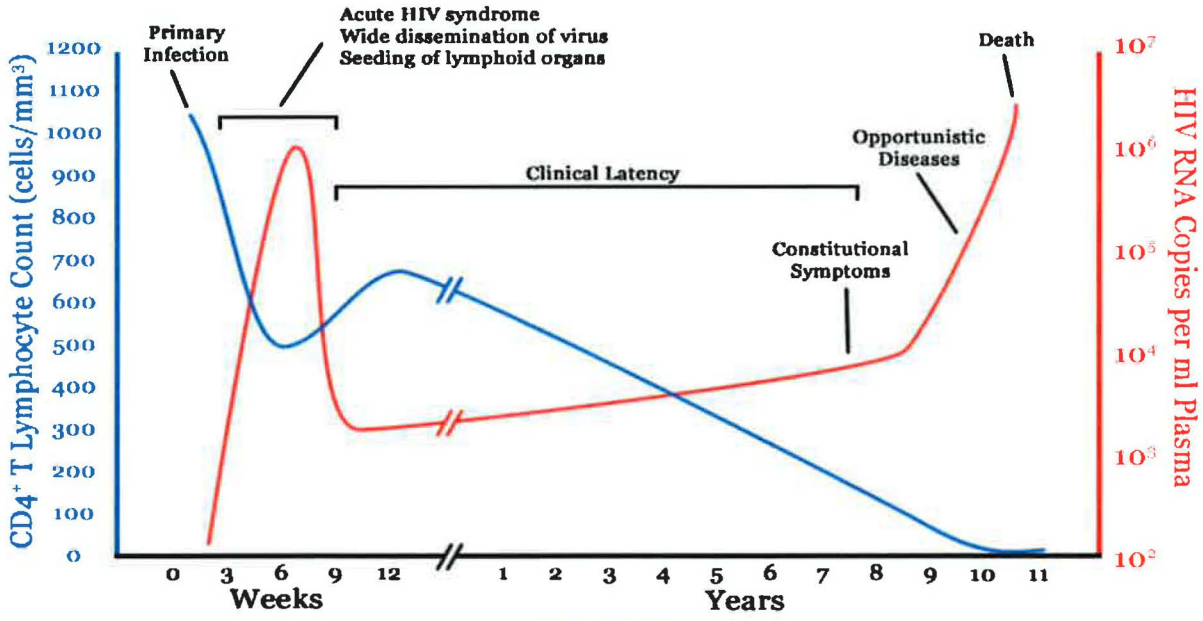


Figure 3 (4)

Figure 3(4) represents the natural progression of HIV infection/disease. As the CD4+ T-cell count decreases, the HIV-infected patient becomes more susceptible to serious bacterial infections, viral infections, endemic fungal infections, mycobacterial infections and HIV associated malignancies. Figure 4 (5) is the classic timetable between CD4+ T-cell count and associated opportunistic infections and malignancies.

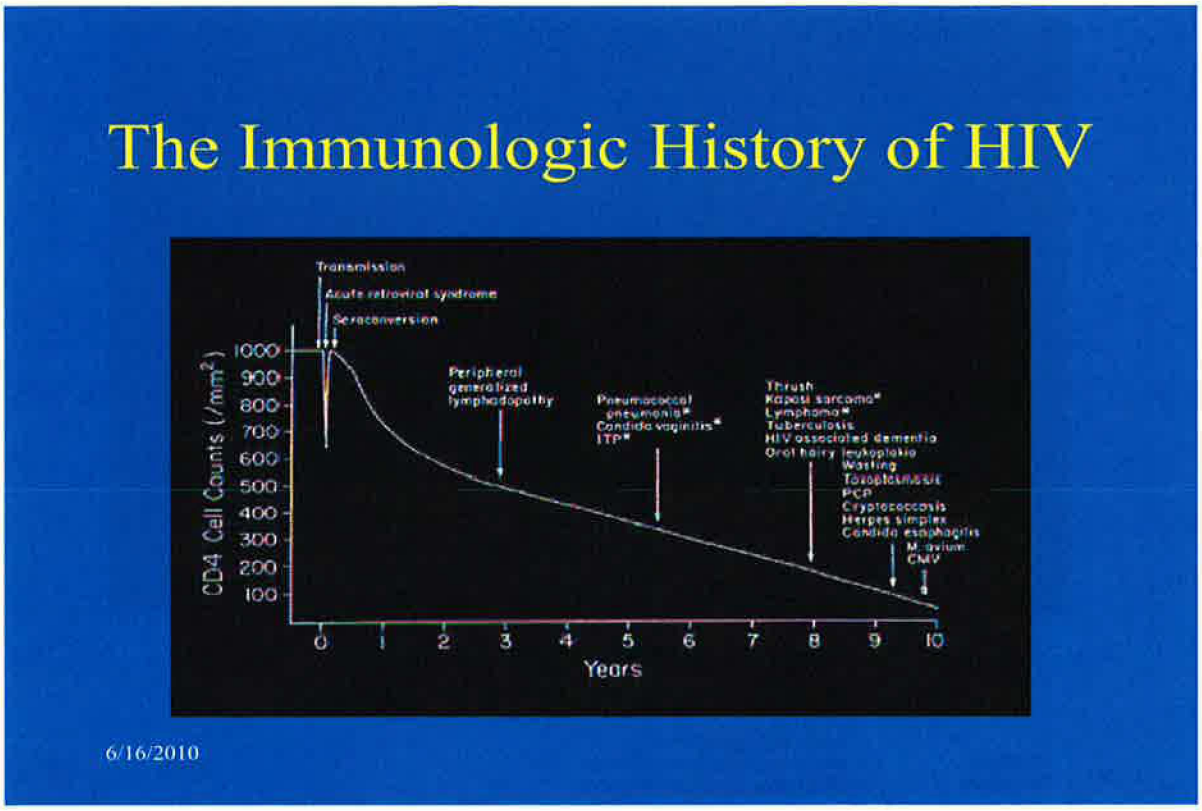
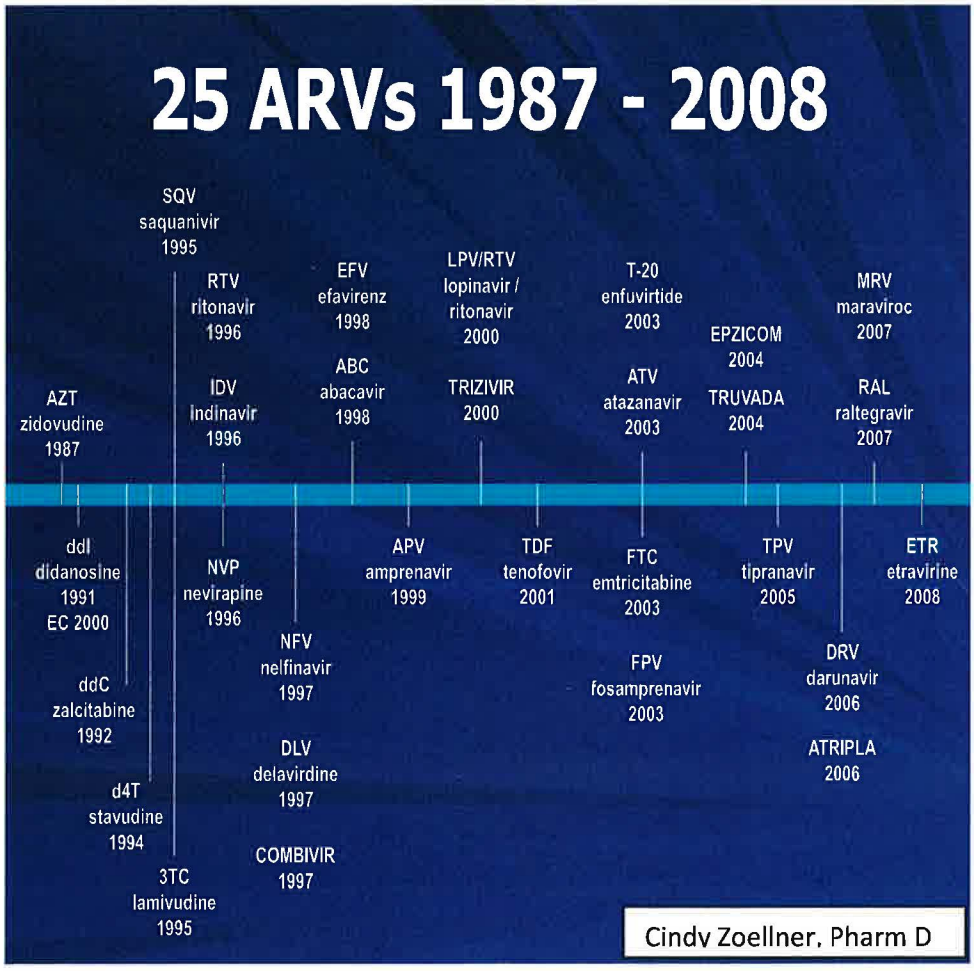
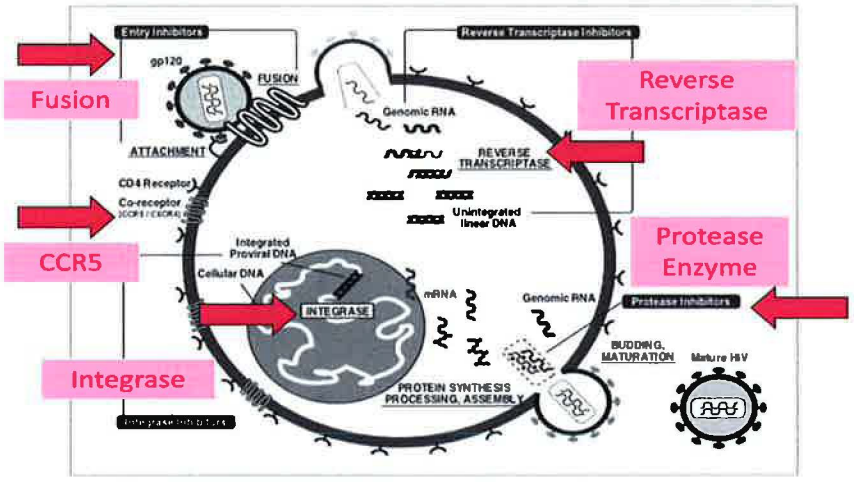


Figure 4(5)

The widespread use of combination HIV medications, known as Highly Active Antiretroviral Therapy (HAART) has had a significant impact on the survival of HIV-infected patients.(6 & 7) Due to the widespread access of antiretroviral therapy in high-income countries, the number of AIDS-related deaths has dropped considerably. In the USA, in 2008, the number of AIDS-related deaths was 25,000.(2) In the USA, in 2007, the number of AIDS-related death was 69% lower than in 1994.(8) There are currently 5 FDA approved classes of HIV medications: Nucleoside Reverse Transcriptase Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Protease Inhibitors, Entry Inhibitors, CCR5 Inhibitors and Integrase Inhibitors

FDA Approved Antiretroviral Agents	
Nucleoside Reverse Transcriptase Inhibitors (NRTI's)	**Protease Inhibitors (PI's)**
❖ Abacavir	• Atazanavir
❖ Didanosine	• Darunavir
❖ Emtricitabine	• Fosamprenavir
❖ Lamivudine	• Indinavir
❖ Stavudine	• Lopinavir/ritonavir
❖ Tenofovir	• Nelfinavir
❖ Zidovudine	• Ritonavir
	• Saquinavir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's)	• Tipranavir
❖ Delavirdine	**Entry Inhibitors**
❖ Efavirenz	• Enfuvirtide
❖ Etravirine	**CCR5 Inhibitors**
❖ Nevirapine	• Maraviroc
	Integrase Inhibitors
	• Raltegravir





http://www.aidsinfonyc.org/tag

Figure 5 (9)

Figure 5(9) Schematically depicts the actions of the 5 classes of HIV medications and their mechanisms of action. HAART is the combination of at least three antiretroviral drugs that attack different parts of HIV or stop the virus from entering blood cells.

DNA bases (-adenosine, guanine, cytosine and thiamidine) are phosphorylated intracellularly to triphosphate to be incorporated into viral DNA via viral RNA dependent DNA polymerase (-reverse transcriptase). The Nucleoside Reverse Transcriptase Inhibitors prevent this from occurring producing viral DNA that is incorrect and incapable of infecting other cells. The Non-Nucleoside Reverse Transcriptase Inhibitors inhibit reverse transcriptase directly by binding to the enzyme and interfering with its function. The Protease Inhibitors target viral assembly by inhibiting the activity of protease, the enzyme used by HIV to cleave nascent proteins for final assembly of new virions. Integrase inhibitors inhibit the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell. Entry Inhibitors (or fusion inhibitors) interfere with binding, fusion and entry of HIV-1 into the host cell by blocking one of several targets.

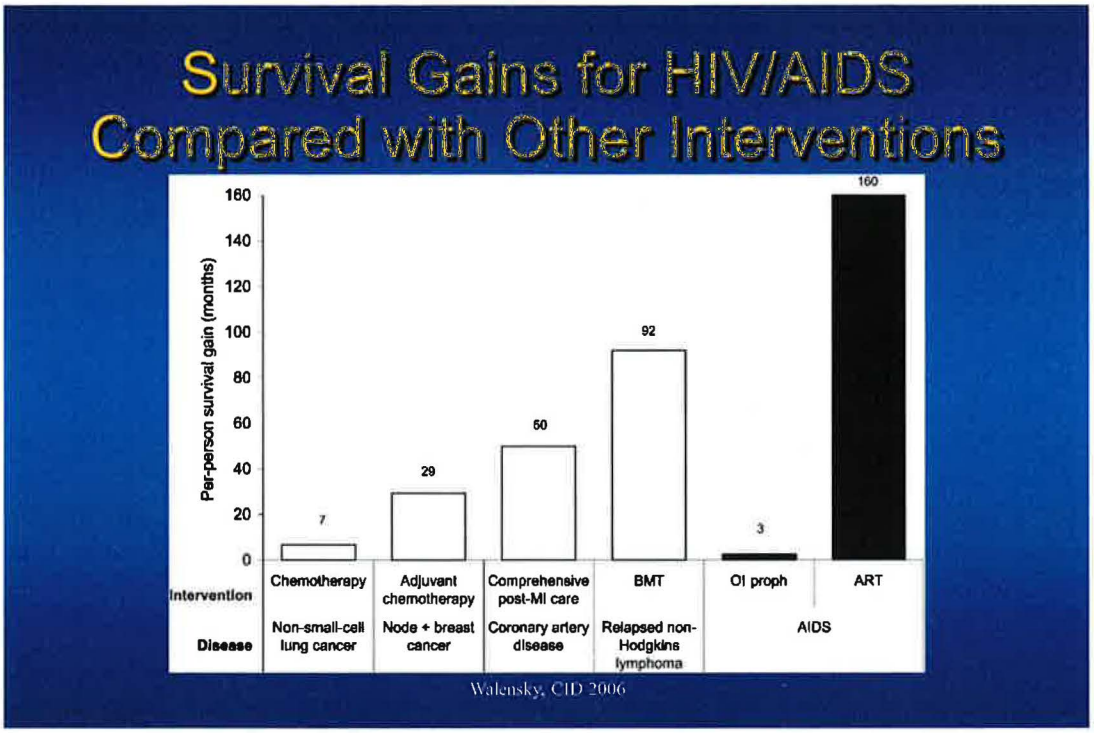


Figure 6 (10)

NEW MORBIITY AND MORTALITY

Life expectancy after HIV diagnosis based on national HIV surveillance data from 25 states in the United States has been published. (11) The following data represents approximately 30% of all AIDS cases diagnosed among adults and adolescents in the United States during 1996-2005. (8) Data from states with high AIDS mortality (eg, California and New York) were not included (11) Excess mortality remains in the HIV-diagnosed population compared with the U.S. general population. (11) Behavioral risk factors and socioeconomic factors may impact morality. And HIV-infected persons have been found to smoke, consume alcohol, and inject drugs and are infected with hepatitis C at higher rates than the general population (11) Nonetheless, average life expectancy after HIV diagnosis in 25 states increased from 10.5 years in 1996 to 22.5 years in 2005. (11) This may very well reflect the use of HAART. Over this 10 year period (1996 to 2005), life expectancy increased 15 years for white males, 13 years for Hispanic males and 10 years for black males. HIV-related mortality is decreasing and this population is dying from causes similar to those of the same age group in the general population (11).

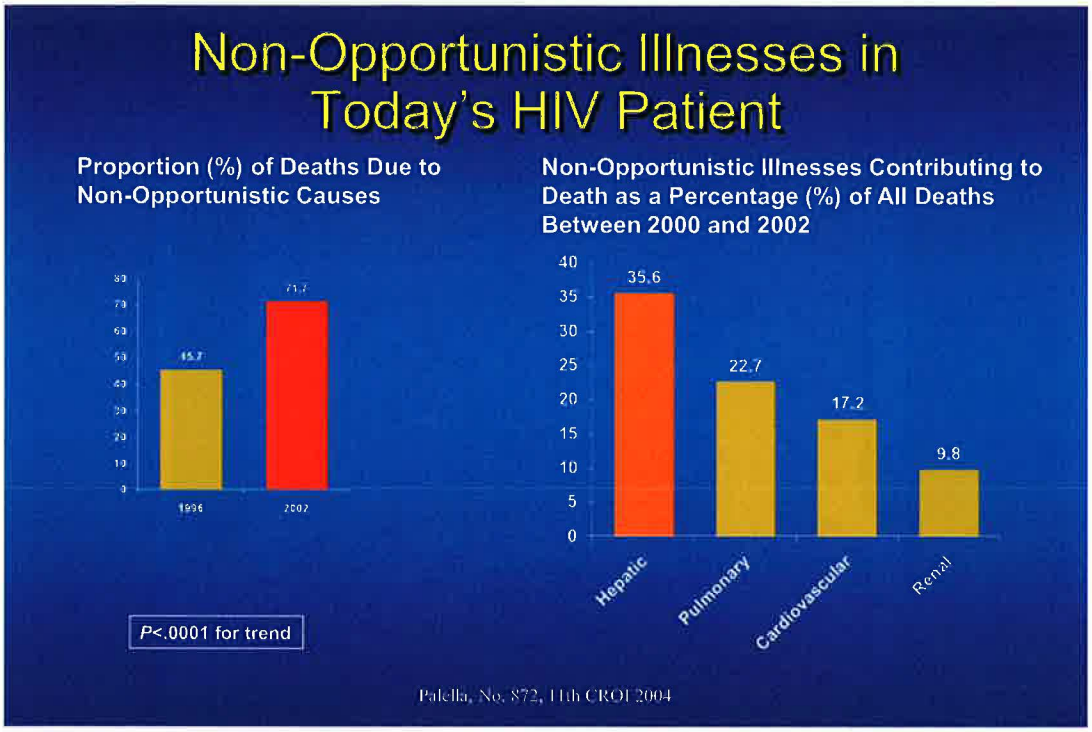


Figure 7

The HOPS (-HIV Outpatient Study) is an ongoing prospective observational cohort study in which patients have been continuously recruited and followed since 1993. (12) Study sites are 12 clinics (7 universities, 3 public and 2 private) in the 10 U.S. Cities that provide care for about 3000 HIV-infected patients per year. (12) HIV-infected patients have more prolonged survival which has allowed chronic underlying co morbid conditions to become more clinically relevant, particularly liver disease (especially chronic co-infection with viral hepatitis), hypertension, diabetes, cardiovascular illness, and pulmonary disease and non-AIDS malignancies. (12) During the period, 2000-2004, non-AIDS death causes included hepatic, pulmonary and cardiovascular illnesses, as well as renal disease and non-AIDS malignancies. In addition, there are unfortunately many sides effects of HAART, including metabolic issues (hyperlipidemia, hyperglycemia, insulin resistance), hepatic toxicity and renal toxicity, which may contribute to non-AIDS morbidity and mortality.

In 2005, France published a multicenter national survey of causes of death among HIV-infected adults in France. (13) Wards that participated in this French study represented around 78,000 HIV-infected patients.(13) In 2005, there were 1042 death (13) The most frequent causes of death were an AIDS-defining illness (13) There were 154 liver-related death: 37 due to hepatocarcinoma (HCV:28, HBV:6, HCV and HBV:3, 89 end stage liver disease due to HCV, 11 end stage liver disease due to HBV, and 11 alcohol related. (13). In addition, there were 88 cardiovascular related deaths: 33 related to coronary

artery disease, 22 due to stroke, 12 due to heart failure, 6 due to pulmonary hypertension, 5 due to venous thrombosis, 4 due to valvular disease, 2 due to arterial thrombosis, 1 due to aortic aneurysm and 2 due to other causes (13). The risk of cardiovascular disease increased with longer exposure to protease inhibitors. (13).

Selik's Trends in Diseases Reported on U.S. Certificates That Mentioned HIV Infection, 1987-1999, reported the following most prevalent conditions mentioned on death certificates: (1) pneumonia organism unspecified, 2320 cases, 14.4%; (2) sepsis, 2270 cases, 14.1%; (3) liver disease including viral hepatitis, 1822 cases, 11.3%; liver disease other than viral hepatitis, 1432 cases, 8.9%, viral hepatitis, 1017 cases, 6.3%; (4) kidney disease, 1664 cases, 10.4%; renal failure, 1599 cases, 10%; (5) heart disease, 1229 cases, 7.7%; ischemic heart disease, 335 cases, 2.1%, heart failure, 265 cases, 1.6%, cardiomyopathy, 260 cases, 1.6%. (14) Wasting/cachexia documented in 1031 cases, 6.4%: (14) Liver disease and heart disease became the third, fourth and fifth most commonly reported conditions by 1999, ahead of HIV-associated wasting/cachexia. (14)

AIDS mortality has decreased markedly. (15) In developed countries, this once fatal infection is now being treated as a chronic condition. As a result, rates of morbidity and mortality from other medical conditions leading to end-stage liver, kidney and heart disease are steadily increasing in individuals with HIV. (15) End-stage cardic, liver and kidney disease have replaced opportunistic infections as the major causes of morbidity and mortality among HIV-infected patients with access to HAART. (15) Unfortunately, HAART agents can induce insulin resistance, diabetes mellitus, hyperlipidemia and subsequent hypertension, all of which are major risk factors for ESRD in the U.S. (15)

TRANSPLANTATION:

Presence of HIV infections used to be viewed as contraindication to transplantation for multiple reasons: concerns for exacerbation of an already immunocompromised state by administration of additional immunosuppressants; the use of limited supply of donor organs with unknown long-term outcomes; and, the risk of viral transmission to the surgical and medical staff. In a 1997 survey of directors of U.S. renal-transplantation centers, 88 percent of respondents indicated that they would not consider transplanting an organ in a patient with asymptomatic HIV-infection who was otherwise a good candidate for transplantation.(16) Only a small group of U.S. transplantation centers agreed to

participate in a multicenter study of transplantation in HIV-infected patients. In the 1997 survey, the opposition was based primarily on concern that transplantation would be harmful to the individual and nearly half the centers also believed that transplanting such patient would be a waste of precious organs.(16) Physicians have been concerned that surgery itself might accelerate the progression of HIV disease.(17) However, there is evidence that disease progression is unaffected by surgery, even major surgery requiring cardiac bypass.(17) Another concern was that HIV-infected patients might transmit the virus to members of the transplantation team. However, the risks of patient to surgeon transmission of HIV is extremely low and is substantially lower than the risk of transmission of many other infectious diseases, including HCV, which is present in many patients who undergo surgery.(17) The occupational transmission rates continue to be highest with hepatitis B, then hepatitis C and lowest with HIV.

AIDS mortality has decreased markedly because of HAART. We have also improved vastly in our prophylaxis of opportunistic infections

Table 1: Opportunistic infection prophylaxis

Pathogen	Indication for prophylaxis	Regimen
Pneumocystis carinii (PCP)	1: All patients indefinitely	Trimethoprim-sulfamethoxozole double-strength 1 tablet daily
	2: All patients indefinitely	
Cytomegalovirus (CMV)	1: All patients for 3 months	Valganciclovir 900 mg daily or ganciclovir 1g three times daily
	2: For 1 month post-transplant or rejection, or when CD4 < 100	
Candida	1: All patients for 1 month	Fluconazole 100 mg weekly[1]
Toxoplasmosis	1: If IgG positive, CD4 <200	Trimethoprim-sulfamethoxozole double-strength 1 tablet daily
	2: For 1 month post-transplant or rejection, or when CD4 < 200	
Mycobacterium avium complex (MAC)	1: When CD4 < 75	Azithromycin 1200 mg weekly
	2: For 1 month post-transplant or rejection or when CD4 < 75	
Epstein-Barr virus (EBV)	1: When recipient serology is negative and donor serology is positive	Ganciclovir 5 mg/kg IV daily, then 1 g three times daily for 1 year
Cryptococcus, extrapulmonary	1: No therapy	Fluconazole 200 mg daily[a]
	2: For 1 month post-transplant or rejection, or when CD4 < 200	
Histoplasmosis	1: No therapy	Itraconazole 200 mg twice daily[a]
	2: All patients regardless of CD4 count	

1 = indicates primary prophylaxis, when no history of infection with pathogen exists; 2 = indicates secondary prophylaxis, when a history of treated infection with pathogen exists.
[a]calcineurin inhibitor and sirolimus dosing must be reduced by at least 50% when azole antifungals used.

(18)

In developed countries, this once fatal infection is now being treated as a chronic condition. As a result, rates of morbidity and mortality from other medical conditions leading to end-stage liver, kidney and heart disease are steadily increasing in individuals with HIV. With the advent of HAART and improved outcomes in HIV-infected patients due to better control of both HIV infection and opportunistic infections, patients with HIV have been reconsidered for transplantation in some

centers, in many cases, as part of an ongoing multicenter NIH sponsored clinical trial investigation solid organ transplantation in HIV-infected patients.

A number of both retrospective and prospective studies have been published providing much needed data on solid organ transplantation in well controlled HIV-infected patients. I will concentrate on renal and liver transplantation in the HIV-infected patient.

RENAL TRANSPLANTATION/LIVER TRANSPLANTATION:

Kidney transplantation is known to improve survival in ESRD.(19) Patients with chronic renal failure have dramatically higher rates of cardiovascular morbidity and mortality than the general population. (19) Cardiovascular mortality increases 10-fold in patients with ESRD.(19) Renal transplantation has been shown to confer a significant survival advantage over maintenance dialysis.(19)

The annual direct costs for ESRD are 23 billion.(19) Compared with maintenance dialysis, renal transplantation has been shown to reduce overall lifetime health care cost along with increasing patient benefit.(19)

Hemodialysis (HD) and peritoneal dialysis (PD) are expensive medical treatments. The 2006 US Renal Data System Annual Data Report noted that the mean annual per-patient costs of dialysis (all modalities) were $67,000 for Medicare patients and $180,000 for patients covered by private health insurance ("Employer Group Health Plans") (20) In 2005, annual per-patient Medicare expenditures related to vascular access were $52,734 for patients with PD catheters and approximately $65,509 for patients with HD access (arteriovenous fistulas, grafts and catheters).(20)

Dialysis is one of the most expensive health interventions for which reimbursement is provided.(19) Although the initial cost of renal transplantation may be higher, after 2 to 3 postoperative years, renal transplantation becomes a cost-saving intervention when compared with dialysis, even considering the cost of maintenance immunosuppression.(19)

In 2002, the CDC issued a report titles: National Surveillance of Dialysis-Associated Diseases in the United States.(21) 4035 centers reported to the survey.(21) The total number of patients being

dialyzed at these centers was 263,820.(21) In 2002, in the United States, there were 1556 (39%) dialysis centers treating patients with HIV infections; 4019 (1.5%) HIV-infected patients and 1055 (0.4%) patients with clinical AIDS.(21) In 2002, since a minority of hemodialysis centers routinely tested for HIV, these figures were probably underestimated.(21)

In summary, it is believed that nearly 1% of all patients with ESRD in the United States and Europe are HIV-infected. (21)

TABLE 8. Chronic hemodialysis centers reporting patients with HIV infection, 1985–2002, United States

Year	No. (%) of centers treating patients with HIV infection	No. (%) of patients with HIV infection	No. (%) of patients with clinical AIDS
1985	134 (11)	244 (0.3)	—
1986	238 (18)	546 (0.6)	332 (0.4)
1987	351 (24)	924 (1.0)	462 (0.5)
1988	401 (25)	1253 (1.2)	670 (0.6)
1989	456 (26)	1248 (1.0)	663 (0.5)
1990	493 (26)	1533 (1.1)	739 (0.5)
1991	601 (29)	1914 (1.2)	967 (0.6)
1992	737 (34)	2501 (1.5)	1126 (0.7)
1993	792 (34)	2780 (1.5)	1350 (0.7)
1994	914 (37)	3144 (1.5)	1593 (0.8)
1995	1022 (39)	3090 (1.4)	1606 (0.7)
1996	1088 (39)	3112 (1.4)	1512 (0.7)
1997	1214 (39)	3298 (1.3)	1501 (0.6)
1999*	1241 (36)	3223 (1.4)	1077 (0.5)
2000	1352 (37)	3447 (1.5)	893 (0.4)
2001	1434 (37)	3822 (1.5)	968 (0.4)
2002	1556 (39)	4019 (1.5)	1055 (0.4)

(21)

TABLE 9. Chronic hemodialysis centers reporting patients with HIV infection/AIDS, by ESRD network, 2002, United States

ESRD network	States, districts, or territories	No. of centers	No. of patients	Percent of patients: HIV infection	Percent of patients: AIDS
1	CT, MA, ME, NH, RI, VT	135	9363	1.6	0.4
2	NY	231	19,553	3.3	1.0
3	NJ, PR	130	11,282	2.5	0.8
4	DE, PA	217	11,770	1.6	0.4
5	DC, MD, VA, WV	269	16,118	3.4	0.5
6	GA, NC, SC	420	25,168	2.1	0.6
7	FL	254	15,765	2.8	0.6
8	AL, MS, TN	273	14,290	1.2	0.4
9	IN, KY, OH	288	18,933	0.5	0.2
10	IL	142	11,504	1.4	0.3
11	MI, MN, ND, SD, WI	293	15,601	0.8	0.4
12	IA, KS, MO, NE	195	9062	0.7	0.2
13	AR, LA, OK	240	11,427	1.1	0.3
14	TX	293	22,240	1.0	0.3
15	AZ, CO, NM, NV, UT, WY	193	11,082	0.4	0.1
16	AK, ID, MT, OR, WA	111	6476	0.3	0.1
17	AS, GU, HI, CA (northern)	142	13,337	0.7	0.2
18	CA (southern)	216	20,717	0.7	0.2
	All	4035	263,820	1.5	0.4

AS, American Samoa; GU, Guam.

(21)

There are several causes of renal diseases in the HIV-infected patient. Possibilities include: HIV associated nephropathy (HIVAN), immune-complex diseases, thrombotic microangiopathy, viral hepatitis associated glomerulonephritis and renal insufficiency from the nephrotoxic effects of: antiretrovirals, antimicrobials, etc. (19) HIVAN is currently the third most common etiology of ESRD among African Americans aged 20-64 years after diabetes and hypertension. (15)

The presence of chronic kidney disease among HIV-infected patients is approximately 17%, and chronic kidney disease is associated with older age, advanced HIV infection, metabolic and vascular diseases, and the use of certain HIV medications (indinavir, tenofovir, etc.) (22)

HIVAN is characterized by heavy proteinuria and high rates of progression to ESRD. (22)

African-American patients with advanced HIV infection are at increased risk of developing ESRD and an "epidemic" of ESRD has long been recognized in this population.(22) Patients with HIVAN, compared with those with other renal diagnoses, have more rapid progression to ESRD, and early HAART initiation may reduce the incidence of HIVAN.(22) Among African Americans, the risks of requiring permanent renal replacement therapy (dialysis) was 16.2 fold higher for those with AIDS and 6.7 fold higher for HIV patients without AIDS, compared with those without HIV infection. (22) Among African-Americans, HIV and diabetes mellitus confer similar risks of developing ESRD compared with white patients HIV infection is not associated with an increases risk of ESRD. (22)

The fact that HIVAN is the third most common etiology of ESRD among African-Americans aged 20-64 years (after diabetes and hypertension) reflects the growing number of HIV-infected African Americans. Although, African American represents 12% of the population in the USA, they accounted for 46% of HIV prevalence and 45% of new HIV infections in 2006. (8) In a large cohort of HIV-infected African-Americans followed up in Baltimore over 15 years, the incidence of ESRD was 1% per year, representing a 10-fold higher risk than the general African American population (23). The prevalence of HIV and ESRD in the United States is expected to rise in the future as a result of the expansion of the AIDS population among African-Americans.(34)

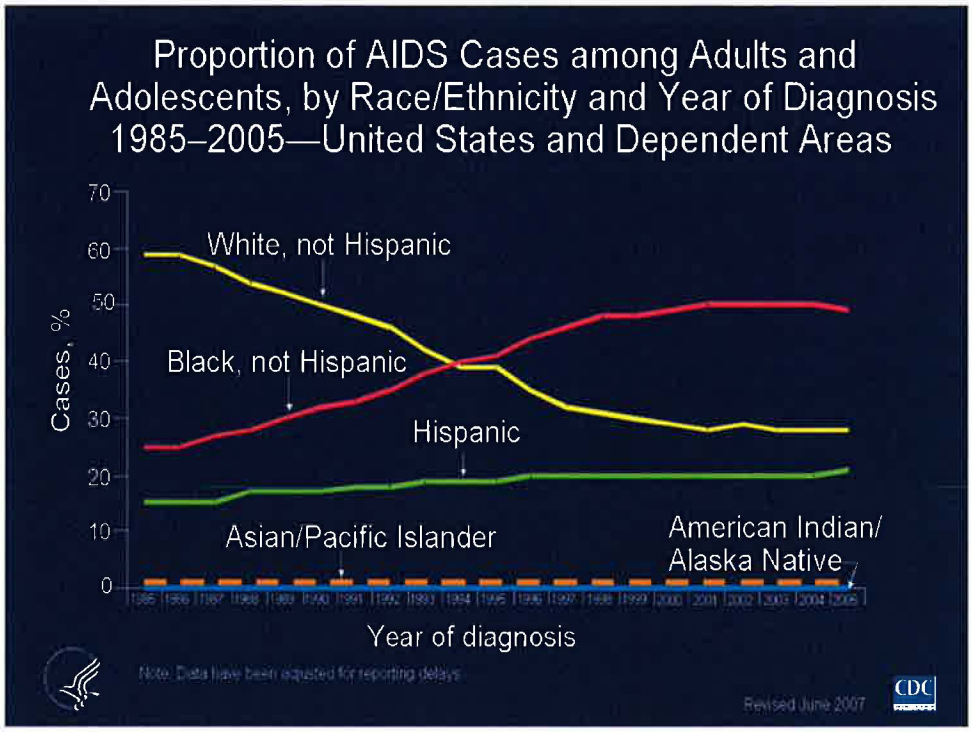


Figure 8 (24)

In the general population, chronic kidney disease (CKD) has been recognized as a significant independent risk factor for mortality.(23) Recent studies have noted CKD to increase mortality significantly in HIV populations.(23) Mortality rates for HIV-infected patients on dialysis were initially quite high, approaching nearly 70% in 1991 and subsequently decreasing to 24% to 2002 (23) In a review of the United States Renal Database System, the 1-year survival of HIV-infected dialysis patients improved from 56% in 1990 to 74% in 1999, which was attributed to the use of HAART. (23) There was no difference in survival between the hemodialysis and peritoneal dialysis groups. (23)

A 2007 study, titled: *Survival during Renal Replacement Therapy among African Americans Infected with HIV Type 1 in Urban Baltimore, Maryland*, found some disturbing results. Not surprisingly, higher CD4 cell count was a significant predictor of survival during renal replacement therapy (dialysis). (24) However, survival for those undergoing renal replacement therapy remains significantly lower in the HIV-infected patient vs the non-HIV infected patients. (24) In their study, the 1-year and 2-year survival during HAART era was 64% and 54%, respectively, which was significantly lower than the reported 80% and 68%, respectively, in the non-HIV-1 infected African American undergoing dialysis.

(24) Therefore, other therapeutic modalities (renal transplantation) need to be pursued to improve the health of this very vulnerable population.

Unfortunately, the antiretrovirals and antimicrobials that our HIV-infected patients receive may also contribute to renal insufficiency. For example, the protease inhibitors, indinavir can contribute to crystal formation and the nucleoside reverse transcriptase inhibitor, tenofovir can cause proximal tubular dysfunction. Tenofovir can cause proximal tubular dysfunction resulting in: reduced phosphate re-absorption, hypophosphatemia and renal tubular acidosis.(22) The most severe form of tenofovir's proximal tubular injury results in a Fanconi-like syndrome with: phosphaturia, glycosuria and aminoaciduria. (22) Tenofovir is a very commonly used HIV medication; elevations in serum creatinine are seen in 2.2% of patients; serious renal adverse events are seen in 0.5% of patients. (22) Boosted protease inhibitors appear to increase the nephrotoxic potential of tenofovir. (22)

Historically, outcomes in HIV-infected patients who received transplant prior to HAART were generally poor when compared to patients without HIV-infectious. (25) Courses were marked by increase development of opportunistic infections and more rapid progression to AIDS. (25)

Most of the published clinical experiences of solid organ transplantation in HIV-infected patients have posted similar inclusion and exclusion criteria. The NIH-multicenter prospective trial is ongoing. Standard criteria for transplantation in HIV-infected individuals are noted in following.(25)

<u>HIV related criteria:</u>
CD4 count >200 cells/uL (kidney patients)
CD4 count >100 cells/uL for liver candidates
Undetectable HIV viral load
If intolerant of antiretrovirals due to severe liver disease, must have genotype/phenotype predictive of viral suppression with HAART
Stable antiretroviral regimen
Absence of active opportunistic infection and malignancy history
- **Patients with history of opportunistic infection and/or malignancy may be considered if all signs/symptoms resolved with appropriate disease free period (period varies with disease)**

<u>Absolute contraindications:</u>
Progressive multifocal leukoencephalopathy
Chronic intestinal cryptosporidiosis (> 1 month duration)
Lymphoma
Other neoplasms with exception of resolved Kaposi's sarcoma, squamous cell carcinoma of skin,

anogenital carcinoma *in situ*, other solid tumors that are considered cured, or hepatocellular carcinoma (liver transplant only)

Miscellaneous:

Absence of chronic wasting or severe malnutrition
Hepatitis C and/or chronic Hepatitis B infection
Liver Biopsy without evidence of advanced fibrosis or cirrhosis (unless combined liver transplant anticipated)
Acceptance of lifelong *Pneumocystis* prophylaxis
Appropriate follow-up by providers experienced in management of HIV infected individuals
Ready access to drug level monitoring

There is currently widespread use of HAART in North America and Europe. Prospective studies form a pilot study of transplantation in HIV-infected patients as well as preliminary results of the NIH sponsored multicenter trial have suggested that 1 year patient and graft survival following kidney transplantation is comparable to that following transplantation in uninfected individuals greater than 65 years of age. (25)

The graft and patient survival rates for renal transplantation and (liver transplantation) in Non-HIV infected patients are the following.(26)

Table 1.13

Unadjusted Graft and Patient Survival at 1 Year, 3 Years, 5 Years, and 10 Years Survival (%)

	Follow up Period			
Organ and Survival Type	1 Year	3 Years	5 Years	10 Years
	TX 2005-2006	TX 2005-2006	TX 2001-2006	TX 1996-2006
Kidney: Decreased Donor Graft Survival	90.4%	79.3%	68.2%	42.3%
Patient Survival	95.0%	88.5%	81.0%	60.9%
Kidney: Living Donor Graft Survival	95.6%	88.9%	80.7%	58.3%
Patient Survival	98.2%	95.1%	90.6%	77.0%
Liver Decreased Donor Graft Survival	82.4%	73.4%	67.6%	53.4%
Patient Survival	87.1%	78.7%	73.3%	59.5%
Liver Living Donor Graft Survival	84.8%	78.1%	70.9%	63.3%
Patient Survival	89.9%	84.6%	77.3%	70.8%

Kumar et al, in 2005, reported on a series of 40 HIV-infected ESRD patients transplanted at a single center in Philadelphia, PA, between 2001 and 2004.(27) The mean follow-up time was 20.4 months, with a 1-year patient survival rate of 85% and a 1-year allograft survival rate of 75%.(27) Patients were given basiliximab induction and maintained on triple immunosuppression with cyclosporine, sirolimus and steroids.(27) Protocol surveillance biopsies were performed, with acute rejection

diagnosed in 22% of patients and subclinical acute rejection in 29%(27) In contrast to other studies, some patients did experience temporary increases in their viral loads, but with alterations in ART regimens all patients were able to achieve viral suppression.(27) Of the 7 patients who died during the study period, 3 died from infections, but none were directly attributable to HIV disease.(27)

In a multicenter pilot study initiated by University of California, San Francisco, Roland et al, in 2008, 18 HIV-infected patients who received renal transplants were followed up for a median of 4 years.(33) They found 1- and 3- year recipient survival rates of 94% and 1- and 3- year allograft survival rates of 83%.(33) None of the 4 patient deaths observed were the result of HIV-related causes.(33) Four renal allografts were lost within the first year, 2 because of chronic rejection, 1 because of acute rejection and 1 because of vascular thrombosis.(33) In total, there were 17 documented episodes of renal allograft rejection, with a 1-year incidence of 52%.(33) There was no progression of HIV disease observed.(33)

In all the published literature as of 2006, in HIV-infected patients status post renal transplant, only 3 patients developed an AIDS-defining opportunistic infection or neoplasm, including a case each of cytomegalovirus and Candida esophagitis, and a third patient with Kaposi's sarcoma/multicentric Castleman's disease.(28)

Unexpectedly high rejection rates were seen in the early studies of renal transplantation in HIV-infected patients. The etiology of this acute rejection rate is unclear.(15) Is it because of dysregulation of the immune system? Is it because of insufficient immunosuppression? The long term effects of this high acute rejection rate are still to be seen. It is intriguing that HIV-infected patients maintained the capacity to develop significant donor specific immune responses even in the presence of immunosuppressive drugs.(29)

The survival rates in these pilot studies of HIV-infected patients who received renal transplants appear to be superior to HIV-infected patients who remained on dialysis.(23)

Common reasons for liver transplant in both the non-HIV-infected patients and the HIV-infected patients include: Hepatitis C with cirrhosis and alcoholic cirrhosis. Hepatitis C and hepatitis B are relatively common in HIV-infected patients. Approximately 30% of HIV-infected patients have

hepatitis B co-infection.(15) An approximately 10% of HIV-infected patients have hepatitis B co-infection.(15) Up to 240,000 people are estimated to be co-infected with HCV and HIV.(30) Co-infection rates of HIV and HCV are even higher in intravenous drug users and hemophiliacs. (29)

Among individuals with HIV-infections, liver-related death is the most frequent case of non-acquired immunodeficiency (AIDS)-related death, primarily related to complications of chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection, as well as hepatotoxicity associated with antiretroviral therapy and alcohol use.(31) The risk of end stage liver disease (ESLD) among hemophiliacs who are HIV positive is nearly 4-fold greater than that among hemophiliacs who are HIV negative, and liver disease has become the second leading cause of death in this group, after HIV infection.(32)

In co-infected patients, the course of hepatitis C has been shown to be more rapid and aggressive, compared with non-HIV-infected individuals.(29) Moreover, advanced liver disease has become a leading cause of death among HIV-HCV and HIV-HBC co-infected patients.(29) Co-infection with HIV also accelerates occurrence of hepatocellular carcinoma, compared with non-HIV-infected individuals.(29)

With the availability of HAART, the mortality from HIV is declining. It is predicted, however, that mortality from HCV with continue to increase into the future. Although the mechanism by which HIV increases progression to ESLD is not know, HIV up-regulates cytokines, which may increase liver fibrosis and lead to liver disease progression. (32) Treatment with HAART may contribute to hepatotoxicity, yet, in some studies, HAART appears to protect against liver disease progression. (32)

Published in 2003, a multisite analysis of 24 liver transplant recipients with HIV infection from the Universities of Pittsburgh, Miami, California at San Francisco, Minnesota and King's College in London was lead by investigators at the University of Pittsburgh.(32) The majority of HIV-positive subjects were white and male. Among the 24 subjects, the cause of ESLD was HCV infection in 15 subjects, HBV infection in 7 subjects and fulminant hepatitis failure in 3 subjects (in association with nevirapine-induced acute hepatic failure necrosis, acute hepatitis A infection and acute hepatitis B infection.(32) The cumulative survival at years 1,2 and 3 (87%, 73%, and 73%) was similar to age and race matched HIV-negative recipients from the United Network for Organ Sharing (UNOS) database (87%, 82%, and 78%).(32) Although HCV infection was associated with poorer survival, as it is among

HIV-negative transplant recipients, the difference in survival between HCV monoinfected and HCV-HIV co-infected individuals did not reach statistical significance.(32) Survival was poorer among subjects: with post-liver transplant antiretroviral intolerance, post-liver transplant CD4+ T-cell count less than 200 cell/uL, a post liver transplant HIV viral load greater than 400 copies/mL and hepatitis C virus infection.(32) Interferon therapy with and without ribavirin was given empirically to subjects with chronic Hepatitis C infection, either within the first 4 weeks after transplantation or after biopsy evidence of HCV infection recurrence, on the basis of institutional preference. (32) Interferon treatment of HCV causes a transient decline in CD4+ T-cell counts.(28) Six subjects (26.1%) died, five due to end-stage liver disease,-three due to drug hepatotoxicity and antiretroviral intolerance, three complicated by recurrent HCV infection and one due to opportunistic fungal infection.(32)

Currently, inclusion criteria for HIV-infected liver transplant candidate include a CD4+ T-cell count greater than 100 cells/uL and undetectable HIV 1 RNA viral load, for minimum of 6 months.(8) For liver transplant candidates intolerant of antiretroviral agents due to severe liver disease, HIV genotypic and phenotypic testing must be predictive of viral suppression on HAART.(25)

Increased rejection rates after liver transplantation in HIV-infected patients was also seen, but not to the same degree as in renal transplantation in HIV-infected patients.

Survival in the HIV-infected liver transplant patient was largely affected by the indication for transplant; the biggest impact on patient survival was the recurrence of hepatitis C infection with the development of a more rapid progression to cirrhosis.(25)

Lamivudine, emtricitabine, and tenofovir have activity against both HIV and HBV. Unfortunately, lamivudine-resistant HBV can develop within 6 months and is seen in 50% of patients after 3 years of therapy. (30) Adefovir and entecavir are active against only HBV and therefore, do not select for HIV drug resistance mutations. In addition to antiviral, hepatitis B immune globulin remains critical to control viral recurrence after liver transplantation.(30)

MEDICATION ISSUES:

Immunosuppression dosing in HIV-infected transplant recipients is complicated and demands close communication and cooperation between the HIV providers and the transplant team. For example, protease inhibitors and the non-nucleoside reverse transcriptase inhibitors both affect the pharmacokinetics of calcineurin inhibitors (CNIs). Commonly used CNIs include cyclosporine and tacrolimus. Protease inhibitors (PIs) may inhibit cytochrome P450 activity resulting in increased CNI levels whereas; non-nucleoside reverse transcriptase inhibitors (-sustiva/efavirenz)may induce cytochrome P450 activity resulting in lower CNI levels.

Calcineurin inhibitors (-cyclosporine,tacrolimus), mycophenolate mofetil (MMF)and sirolimus have shown antiretroviral activity in vitro. MMF virostatic action is thought to result from the depletion it causes of guanoside nucleosides, which are necessary for virus lifecycle.(15) Cyclosporine and tacrolimus have antiretroviral effects through selective inhibition of infected cell growth.(15) Cyclosporine and tacrolimus interfere with HIV pathogenic protein functions, which result in the reduction of virus formation.(15) CNIs and sirolimus also exerts some antiretroviral activity through suppression of T-cell activation and disruption of infective virons replication.(15) Sirolimus also decreases the expression of chemokine receptor type 5 on monocytes and lymphocytes, thus potentially preventing the HIV virus from entering these cells and replicating.(15)

The immunosuppression regimens in the initial clinical trials of organ transplantation in HIV-infected patients included maintenance therapy of: steroids, a CNI and MMF.(15) HIV-infected renal transplant patients were found to have higher rejection rates than their counterparts without HIV.(15) For this reason, induction therapy with interleukin 2 receptor inhibitor has been introduced.(15) HIV-infected patients typically experience declines in the CD4+ T-cell counts following transplantation, but this does not appear to impact on infection risks.(25)

Pharmacologic interactions were well documented in a study describing the pharmacokinetics/dosing modifications of cyclosporine, sirolimus and tacrolimus in 35 liver/kidney transplants on NNRTs, PIs or both.(15) Pts on PIs and cyclosporine required only 20% of the immunosuppressant dose administered to renal transplant recipients without HIV.(15) PI-ritonavir is often used to increase/boost plasma levels of other PIs. Even low doses of ritonavir significantly inhibit the

cytochrome P450 metabolizing enzymes found in the gut and liver, therefore, patients on a ritonavir-boosted PI regimen required even lower doses of immunosuppressant than patients on other HAART regimens.(15) In patients on tacrolimus or sirolimus, when on a PI based regimen not only was the immunosuppressant dose markedly decreased, but the dosing interval increased more than five-fold.(15)

Azole antifungals and macrolide antibiotics can inhibit the cytochrome P450 metabolizing enzymes. Patients taking steroids are usually taking proton pump inhibitors, which can reduce intestinal absorption of the PI, atazanavir, and thus, the drug's plasma concentration. Atazanavir should be avoided when proton pump inhibitors will be used and it should be used with caution in combination with other antacids. MMF and abacavir may have synergistic anti-HIV-1 activity.(15) MMF may antagonize the antiviral effects of zidovudine and stavudine.(15) MMF could also contribute to the myelosuppressive effects of zidovudine.(15) Interestingly, integrase inhibitor, raltegravir, has little interaction with CNIs.(25)

In general, lymphocyte depleting agents, such as thymoglobulin, have been avoided in induction therapy. Thymoglobulin has been noted to cause a swift, profound and prolonged CD4+ T-cell depletion. Rejection episodes have been treated successfully with corticosteroids and CNI switching in some patients, though thymoglobulin has been used in more severe rejections.

Carter et al., studied thymoglobulin-associated CD4+ T-cell depletion and infection risk in HIV-infected renal transplant recipients. Concerns about the use of thymoglobulin in patients with HIV include prolonged CD4+ T-cell depletion, failure to suppress opportunistic infections, loss of HIV viral control and more rapid progression to AIDS and death.(18) Given that HIV-induced CD4+ T-cell depletion predisposes patients to opportunistic and select non opportunistic infections, there is concern that thymoglobulin-induced CD4+ T-cell depletion may similarly predispose HIV-infected transplant recipients to greater infection risk.(18) In patients without HIV, thymoglobulin produces lymphocyte depletion for as long as 2 years, and may deplete the CD4+ T-cell count for even longer.(18) Such depletion is associated with increased risk of infection.(18) This prospective observational study aimed at characterizing the effect of thymoglobulin on CD4+ T-cell counts, infection rate, HIV viral suppression and success in reversing acute rejection in HIV-infected kidney transplant recipients.(18) The study included 20 consecutive HIV-infected patients who underwent kidney transplantation at a

single center over a 4 year period, and compared the 11 patients who received thymoglobulin with the nine who did not.(18) Maintenance immunosuppression consisted of prednisone, mycophenolate mofetil and cyclosporine.(18) Eleven patients received thymoglobulin (7 for rejection and 4 for delayed/slow graft function) while 9 did not.(18) Mean CD4+ T-cell counts remained stable in patients who did not receive thymoglobulin, but became profoundly suppressed in those who did.(18) Recovery time of CD4+ T-cell counts ranged from 3 weeks to 2 years despite effective HIV suppression.(18) Classic HIV-associated opportunistic infections were not seen with the thymoglobulin induced low CD4+ T-cell counts, but was associated with serious (bacterial) infectious requiring hospitalization.(18) Ten such bacterial infections were observed in six thymoglobulin recipients: Staph aureus endocarditis with septic embolization, Strept viridans bacteremia, Pseudomonas pneumonia with multi-organ failure, Escherichia coli urosepsis, culture-negative urosepsis, Enterococcal bacteremia, polymicrobial nosocomial pneumonia with sepsis, C. difficile colitis, diverticulitis and secondary bacterial peritonitis.(18) All but one of these bacterial infections occurred when the CD4+ T-cell count was less than 200 cells/uL.(18) Time from thymoglobulin administration to first serious bacterial infection ranged from 35-382 days.(18) Rejection reversed in 6 patients receiving thymoglobulin. Carter et al, concluded that thymoglobulin can reverse acute rejection in HIV-infected kidney recipients, but produces profound and long lasting suppression of the CD4+ T-cell count associated with increased risk of serious bacterial infections requiring hospitalization.(18)

CONCLUSION:

When HAART is available and patients are compliant, statistics reflect that HIV-infected morbidity and mortality has shifted away from the classic opportunistic infections and now HIV-infected patients are dealing with medical conditions that plague the HIV-non-infected general population. Diabetes, hypertension, hyperlipidemia, cardiac disease, progression of underlying liver disease often due to hepatitis B and hepatitis C, and renal insufficiency are often encountered in the HIV Clinic. In fact, in recent years, opportunistic infections have been replaced by chronic kidney, liver and cardiac disease as leading causes of mortality in HIV-infected patients on HAART.(29)

Recently, ESRD has been shown to be increased in HIV-infected patients,(29) HIVAN currently represents the third leading cause of ESRD in young African-Americans, and though early HAART may

reduce the incidence of HIVAN, dialysis and/or renal transplantation may represent the only therapeutic options. Advanced liver disease has become a leading cause of death among HIV-HCV and HIV-HBC co-infected patients.(29)

In 2006, UNOS policy did not consider HIV infection to be a contraindication for transplantation. (30) And in 2006, the United States Veterans Affairs Administration had revised its policy to allow transplantation in HIV-infected patients.(30)

Hopefully, the NIH multi-center study enrolling 125 liver and 150 kidney transplant recipients at 20 transplant centers will provide much needed additional information, clinical and scientific, that help manage and treat these complicated patients.(www.HIVtransplant.com)

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