

Background

- Abnormal fat loss or “lipoatrophy” in HIV-1 infection has been associated with the use of nucleoside reverse transcriptase inhibitors. Our previous retrospective prevalence study of lipodystrophy in the HOPS cohort found associations with a number of host and disease factors in addition to medications.
- The objective of this study is to prospectively analyze the factors associated with the development of lipoatrophy in a large cohort of HIV-1 infected patients utilizing data obtained over the entire course of their infection.

HOPS: HIV Outpatient Study Evaluation of Risk Factors for LD

- **HOPS cohort: HIV-infected outpatients from 8 specialty clinics in 7 US cities**
- **Sponsored by the Centers for Disease Control and Prevention (CDC)**
- **Two standardized patient/physician evaluations:**
 - Survey 1 - 1064 patients 4th quarter of 1998
 - Survey 2 - 1244 patients 3rd quarter of 2000
 - 546 patients were in both surveys
- **Data collected**
 - Demographic
 - Clinical
 - Immunologic
 - Virologic
 - Pharmacologic

HOPS Lipodystrophy Patient Classification Definitions

- **Subtle** Noticeable only if specifically looked for
No change in clothing fit
- **Moderate** Easily noted by patient or physician
Clothing has become looser or tighter
- **Severe** Obvious to the casual observer
Has required change in clothing size

HOPS:

Definition of Lipodystrophy

- **None** **No body areas affected**
- **Mild** **1-2 body areas, subtly or moderately affected**
- **Moderate** **3-4 body areas, 1 severely affected**
- **Severe** **5-6 body areas, at least 1 severely affected**

HOPS:

Definition of Lipodystrophy

- The **None** and **Mild** categories were combined to represent **No Lipodystrophy**
- The **Moderate** and **Severe** categories were combined to represent **Presence of Lipodystrophy**

Rationale:

- To minimize misclassification of signs
- To bias the results against finding minimally significant differences

Distribution of patients in the HOPS by Marrakesh Classification

	Survey 1 (N=1064)	Survey 2 (N=1244)	Pts in Both Distrib. At S1 (N=546)	Pts in Both Distrib. At S2 (N=546)
None	37.4% (398)	31.6% (393)	35.1% (192)	21.2% (116)
Atrophy Only	13.4% (143)	19.6% (244)	13.2% (72)	23.8% (130)
Accumulation Only	13.3% (142)	10.1% (126)	12.3% (67)	9.2% (50)
Mixed	22.6% (240)	27.5% (342)	25.1% (137)	35.7% (195)
Metabolic Only	13.3% (141)	11.2% (139)	14.3% (78)	10.1% (55)
Total	100%	100%	100%	100%

New Incidence of Mod/Severe Atrophy Survey 1 to Survey 2 (N=337)

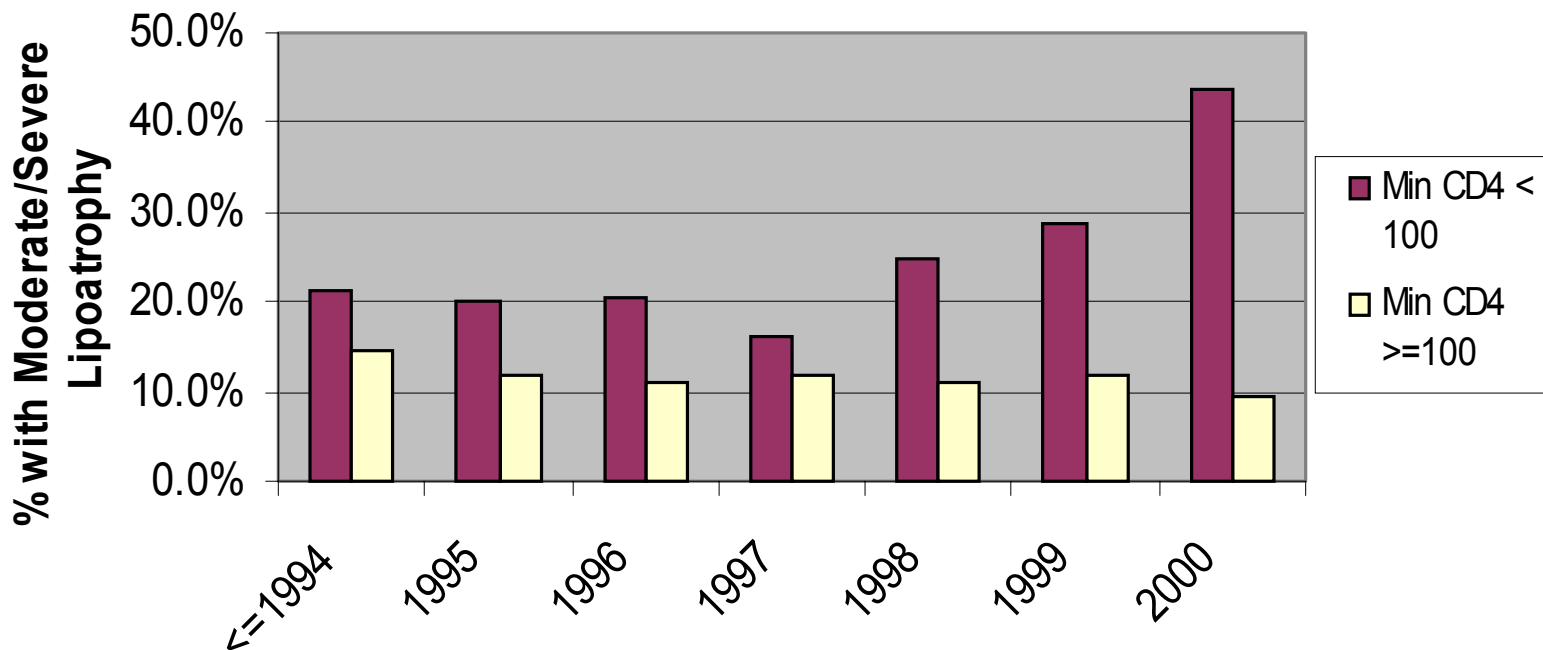
	<u>%</u>	<u>p-value*</u>	<u>Adj OR</u>	<u>95% CI</u>	<u>p-value</u>
<u>Host Factors</u>					
White Race	17.1% (38/222)	0.006	5.03	(1.88-16.71)	0.003
Age >50	18.8% (12/64)	0.577	-	-	-
<u>Disease Factors</u>					
CD4+ cell count at S2 <100 cells/mm ³	43.5% (10/23)	<0.001	4.37	(1.39-13.81)	0.011
CD4+ cell count Δ <50 cells/mm ³	30.2% (16/53)	<0.001	3.16	(1.15-8.42)	0.022
BMI Nadir at S2 <24	52.8% (36/207)	<0.001	3.23	(1.31-9.30)	0.017
Viral burden (logs) at S2 >3	19.0% (23/121)	0.022	-	-	NS
<u>Treatment Factors</u>		NS	-	-	NS

*Cochran-Mantel-Haenszel test, controlling for site and race

Incidence of Lipoatrophy Based on Prior CD4 Cell Counts

Year	<=1994	1995	1996	1997	1998	1999	2000
	7	10	14	8	9	10	14
	33	50	68	50	36	35	32
Min CD4 < 100	21.2%	20.0%	20.6%	16.0%	25.0%	28.6%	43.8%
	21	12	16	28	33	34	27
	145	103	143	239	297	292	285
Min CD4 >=100	14.5%	11.7%	11.2%	11.7%	11.1%	11.6%	9.5%

Proportion of Patients with Moderate/Severe Lipoatrophy by Minimum CD4 For Each Year



Incidence of Lipoatrophy with Measurements of Severity of Illness

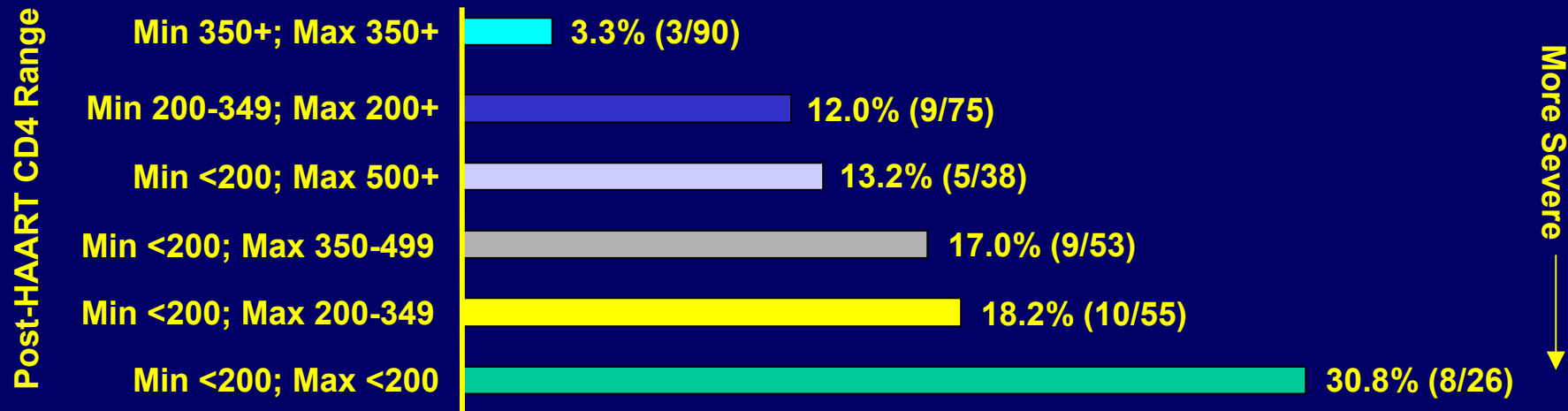
	CD4 Counts						Viral Burden (logs)						Body Mass Index						
Time Period	All Under 100		Varying		All 350 and Over		All Three or More		Varying		All Under Three		All Under 24		Varying		All 26 and Over		
<= 1994	37.5%	(3/8)	13.2%	(40/303)	3.8%	(1/26)								15.2%	(5/33)	13.5%	(39/289)	0.0%	(0/15)
1994-1996	20.7%	(6/29)	14.3%	(37/258)	2.0%	(1/50)	18.8%	(12/64)	10.9%	(24/221)	15.4%	(8/52)	17.5%	(14/80)	11.7%	(25/214)	11.6%	(5/43)	
1996-1999	50.0%	(4/8)	15.7%	(34/216)	5.3%	(6/113)	20.0%	(11/55)	13.4%	(27/202)	7.5%	(6/80)	18.7%	(17/91)	13.3%	(23/173)	5.5%	(4/73)	
2000	53.3%	(8/15)	16.3%	(23/141)	7.2%	(13/181)	19.1%	(18/94)	12.9%	(8/62)	9.9%	(18/181)	19.4%	(24/124)	12.8%	(14/109)	5.8%	(6/104)	

Incidence of Moderate/Severe Lipoatrophy at Survey 2 by Cumulative Time On Antiretroviral Therapy and Disease Severity (Post-HAART CD4 Range)

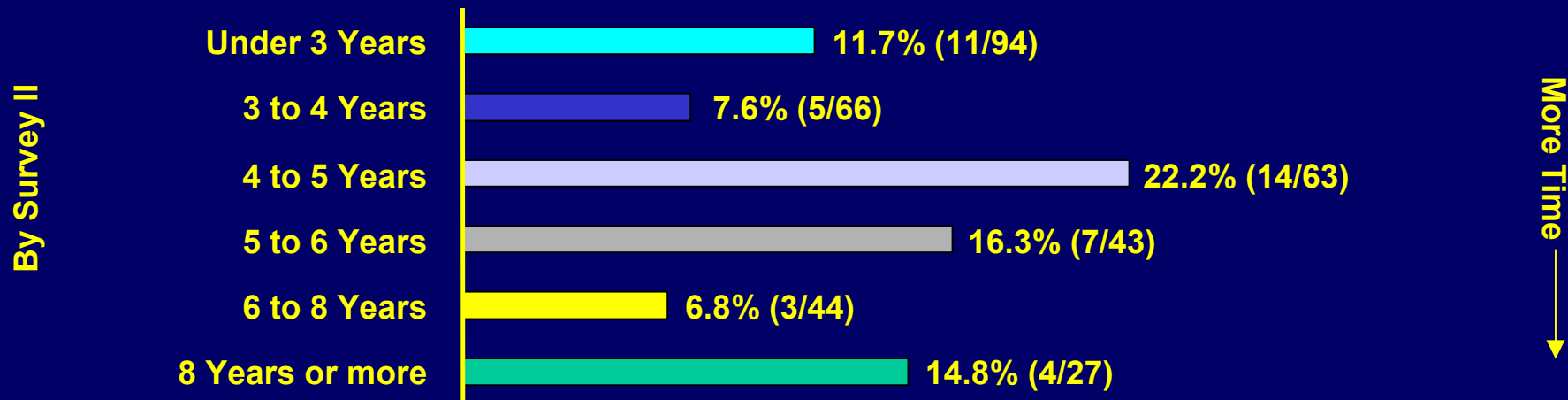
Disease Severity	Cumulative Time on Antiretroviral Therapy By Survey 2						
Cd4 Range	< 3 Yrs	3-4 Yrs	4-5 Yrs	5-6 Yrs	6-8 Yrs	8 + Yrs	Total
Min 350+; Max 350+	4.9% (2/41)	7.7% (1/13)	0.0% (0/13)	0.0% (0/8)	0.0% (0/7)	0.0% (0/8)	3.3% (3/90)
Min 200-349; Max 200+	14.3% (3/21)	0.0% (0/19)	18.2% (2/11)	66.7% (4/6)	0.0% (0/9)	0.0% (0/9)	12.0% (9/75)
Min <200; Max >500	14.3% (1/7)	0.0% (0/6)	30.0% (3/10)	20.0% (1/5)	0.0% (0/8)	0.0% (0/2)	13.2% (5/38)
Min <200; Max 350-499	25.0% (2/8)	6.3% (1/16)	40.0% (4/10)	16.7% (1/6)	11.1% (1/9)	0.0% (0/4)	17.0% (9/53)
Min <200; Max 200-349	0.0% (0/9)	14.3% (1/7)	20.0% (3/5)	10.0% (1/10)	18.2% (2/11)	100.0% (3/3)	18.2% (10/55)
Min <200; Max <200	37.5% (3/8)	40.0% (2/5)	50.0% (2/4)	0.0% (0/8)	--- (0/0)	100.0% (1/1)	30.8% (8/26)
Total	11.7% (11/94)	7.6% (5/66)	22.2% (14/63)	16.3% (7/43)	6.8% (3/44)	14.8% (4/27)	13.1% (44/337)

Patients (%) With New Moderate or Severe Lipoatrophy at Survey II

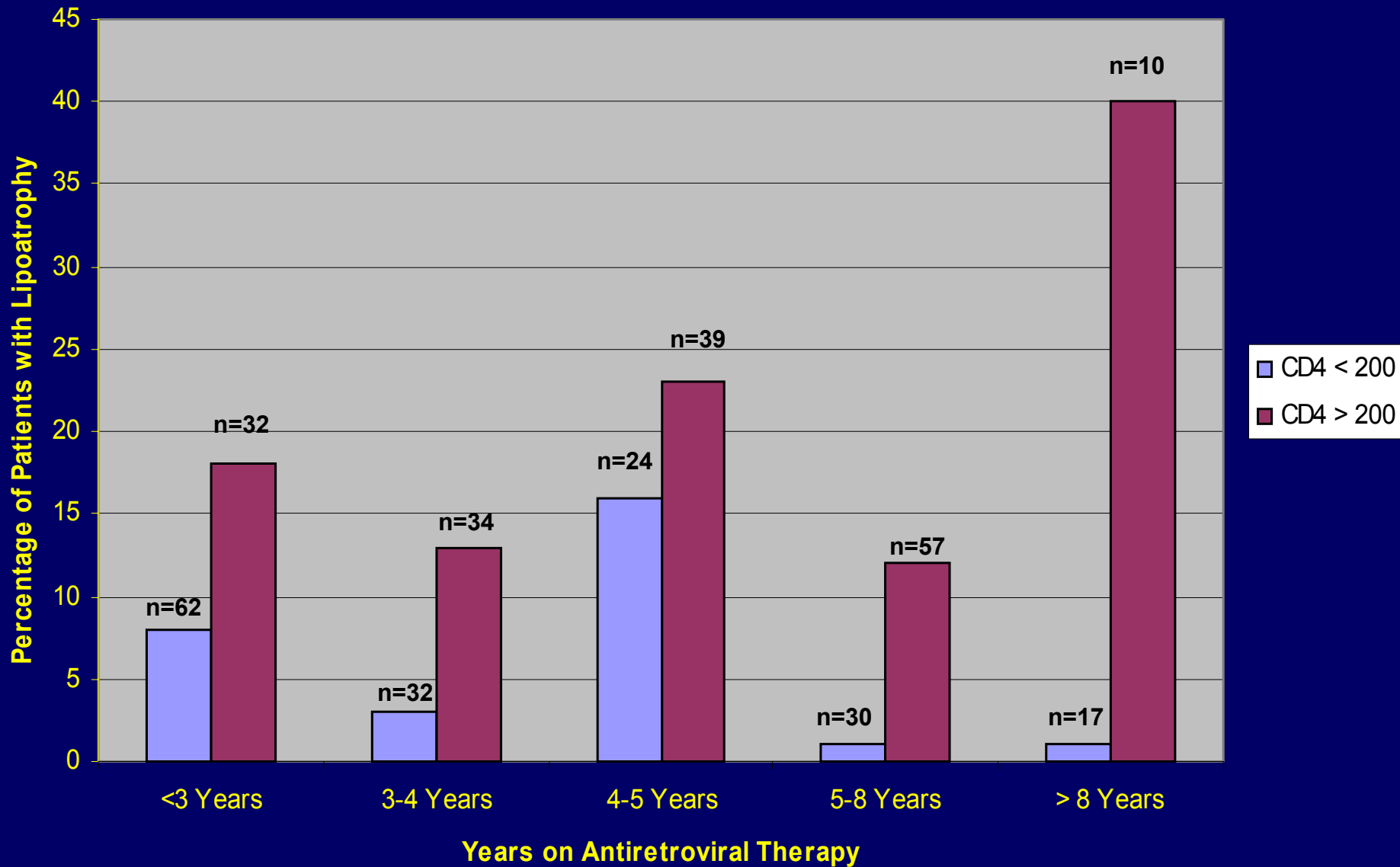
Disease Severity



Time on Antiretrovirals



Lipoatrophy Based on CD4 Count



Incidence of Lipoatrophy CD4 Count vs. Time on ART

Treatment	Cumulative Use by S II	CD4 Count at Survey II							
		<100		100-349		350+		TOTAL	
Zidovudine	None	50.0%	(2/4)	11.8%	(2/17)	11.9%	(8/67)	12.9%	(12/93)
	< 1Y	60.0%	(3/5)	16.7%	(3/18)	10.7%	(3/28)	17.5%	(10/57)
	1Y-2Y	50.0%	(2/4)	25.0%	(3/12)	0.0%	(0/21)	15.0%	(6/40)
	2Y+	30.0%	(3/10)	15.6%	(7/45)	6.9%	(6/87)	10.9%	(16/147)
Stavudine	None	50.0%	(1/2)	13.3%	(4/30)	5.8%	(3/52)	8.5%	(8/94)
	< 1Y	60.0%	(3/5)	8.3%	(1/12)	0.0%	(0/24)	9.8%	(4/41)
	1Y-2Y	42.9%	(3/7)	26.7%	(4/15)	3.7%	(1/27)	15.7%	(8/51)
	2Y+	33.3%	(3/9)	17.1%	(6/35)	13.0%	(13/100)	15.9%	(24/151)
Nevirapine	None	38.5%	(5/13)	14.9%	(10/67)	9.0%	(13/145)	12.1%	(29/239)
	< 1Y	75.0%	(3/4)	28.6%	(4/14)	10.0%	(2/20)	24.4%	(10/41)
	1Y-2Y	50.0%	(2/4)	16.7%	(1/6)	0.0%	(0/12)	12.5%	(3/24)
	2Y+	0.0%	(0/2)	0.0%	(0/5)	7.7%	(2/26)	6.1%	(2/33)
Efavirenz	None	33.3%	(4/12)	8.8%	(5/57)	6.3%	(9/143)	8.0%	(18/225)
	< 1Y	55.6%	(5/9)	29.4%	(5/17)	15.0%	(3/20)	28.6%	(14/49)
	1Y-2Y	50.0%	(1/2)	33.3%	(5/15)	3.0%	(1/33)	15.4%	(8/52)
	2Y+	---		0.0%	(0/3)	57.1%	(4/7)	36.4%	(4/11)

Incidence of Lipoatrophy CD4 Count vs. Time on ART

Treatment	Cumulative Use by S II	CD4 Count at Survey II							
		<100		100-349		350+		TOTAL	
Saquinavir	None	44.4%	(4/9)	12.0%	(6/50)	7.9%	(12/152)	9.9%	(22/223)
	< 1Y	37.5%	(3/8)	23.5%	(4/17)	7.1%	(1/14)	19.0%	(8/42)
	1Y-2Y	66.7%	(2/3)	20.0%	(3/15)	10.5%	(2/19)	22.5%	(9/40)
	2Y+	33.3%	(1/3)	20.0%	(2/10)	11.1%	(2/18)	15.6%	(5/32)
Ritonavir	None	44.4%	(4/9)	12.5%	(6/48)	9.7%	(14/145)	11.2%	(24/215)
	< 1Y	50.0%	(4/8)	32.0%	(8/25)	8.3%	(2/24)	24.6%	(15/61)
	1Y-2Y	33.3%	(2/6)	0.0%	(0/14)	5.6%	(1/18)	10.0%	(4/40)
	2Y+	---		20.0%	(1/5)	0.0%	(0/16)	4.8%	(1/21)
Indinavir	None	40.0%	(2/5)	13.0%	(3/23)	10.5%	(10/95)	11.2%	(15/134)
	< 1Y	33.3%	(2/6)	23.5%	(4/17)	9.1%	(2/22)	18.4%	(9/49)
	1Y-2Y	50.0%	(3/6)	15.4%	(2/13)	4.2%	(1/24)	13.3%	(6/45)
	2Y+	50.0%	(3/6)	15.4%	(6/39)	6.5%	(4/62)	12.8%	(14/109)

Incidence of Lipoatrophy CD4 Count vs. Time on ART

<u>Treatment</u>	Cumulative Use by S II	CD4 Count at Survey II							
		<100		100-349		350+		TOTAL	
Any NRTI	< 2Y	100.0%	(1/1)	25.0%	(2/8)	0.0%	(0/15)	10.3%	(3/29)
	2Y-4Y	66.7%	(4/6)	12.9%	(4/31)	8.3%	(8/96)	12.0%	(17/142)
	4Y-6Y	41.7%	(5/12)	11.4%	(4/35)	16.7%	(8/48)	18.2%	(18/99)
	6Y+	0.0%	(0/4)	27.8%	(5/18)	2.3%	(1/44)	9.0%	(6/67)
Any NNRTI	None	40.0%	(2/5)	12.5%	(5/40)	5.1%	(5/98)	7.8%	(12/153)
	< 1Y	66.7%	(4/6)	15.8%	(3/19)	5.6%	(1/18)	19.6%	(9/46)
	1Y-2Y	42.9%	(3/7)	31.6%	(6/19)	6.4%	(3/47)	16.7%	(13/78)
	2Y+	20.0%	(1/5)	7.1%	(1/14)	20.0%	(8/40)	16.7%	(10/60)
Any PI	None	---		16.7%	(1/6)	17.1%	(6/35)	15.2%	(7/46)
	< 1Y	50.0%	(1/2)	50.0%	(1/2)	0.0%	(0/6)	20.0%	(2/10)
	1Y-2Y	0.0%	(0/1)	11.1%	(1/9)	6.9%	(2/29)	6.8%	(3/44)
	2Y+	45.0%	(9/20)	6.9%	(12/175)	6.8%	(9/133)	13.5%	(32/237)
Any AR	< 2Y	100.0%	(1/1)	25.0%	(2/8)	0.0%	(0/13)	11.1%	(3/27)
	2Y-4Y	50.0%	(2/4)	10.3%	(3/29)	8.7%	(8/92)	9.8%	(13/133)
	4Y-6Y	50.0%	(7/14)	11.1%	(4/36)	15.7%	(8/51)	19.8%	(21/106)
	6Y+	0.0%	(0/4)	31.6%	(6/19)	2.1%	(1/47)	9.9%	(7/71)

Conclusions

- Lipoatrophy appears to have strong associations with measurements of severity of disease (low CD4+ count, high viral load, low body mass index).
- Low CD4+ count or CD4+ range at any time during HIV-1 infection is associated with a higher risk of development of lipoatrophy.
- In this study we were unable to demonstrate a strong association of lipoatrophy with specific antiretroviral medications or duration of treatment.