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LIPODYSTROPHY 20 YEARS AFTER INITIAL DESCRIPTIONS: BODY FAT CHANGES IN PERSONS LIVING WITH HIV IN 2018

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Lipodystrophy 20 Years After Initial Descriptions: Body Fat Changes in Persons Living with HIV in 2018 [video transcript]

[00:00:01] Welcome to Physicians Research Network. I'm Jim Braun the course director of the monthly meetings of PRN in New York City. Since their beginning in 1990 PRN has been committed to enhancing the skills of members in the diagnosis, management, and prevention of HIV disease as well as its coinfections and complications. We hope this recording of Todd Brown's presentation 'Lipodystrophy 20 Years After Initial Descriptions: Body Fat Changes in Persons Living with HIV in 2018' will be helpful to you in your daily practice and invite you to join us in New York City for our live meetings in the future. PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants and membership is open to all interested clinicians nationwide at our website PRN.org. Now allow me to introduce Todd Brown, Professor of Medicine and Epidemiology in the Division of Endocrinology, Diabetes, and Metabolism at the Johns Hopkins University in Baltimore, Maryland.

[00:01:04] Well thanks for the invitation to come speak to you. Usually, I'm an endocrinologist, so I do an endocrine topic and so I thought it was fitting this time around to talk a little bit about body fat. So 20 years ago so 1998, both lipoatrophy and lipohypertrophy were first described. And now as we'll see, in 2018, things have changed quite a bit but there are some new body composition issues that are just emerging in people living with HIV.

[00:01:33] So I never get sick of showing this slide. This is Frank Palella's, known as the 'palella-gram.' So this is his New England Journal paper, the most cited to paper in HIV medicine. So this really is the story of the 90's as far as HIV goes, that what was once the biggest killer in young people became a chronic disease with the use of protease inhibitors in the late 90's. And soon after this as you all know a bunch of different metabolic abnormalities were described.

[00:02:09] And this is where I started to get interested. I was a resident at Georgetown and I was doing an ID rotation and seeing these patients in clinic who were doing great from an HIV standpoint, you know high CD4 cell counts and undetectable viral loads, but they had these metabolic and endocrine problems and and I thought this was really interesting and something that no one really knew what was going on at the time. And at the initial descriptions it was thought that these problems were all linked and they are to a certain degree, but they can also be seen separately. And the first of these body composition changes was peripheral lipoatrophy and this was first described by Andrew Carr and David Cooper. David as you know passed away this year, and he and Andrew and others had done some really pioneering work at the beginning of the issue, to address this issue of lipodystrophy.

[00:03:09] So as we know the body composition changes that were described initially could be best segregated into lipoatrophy and lipohypertrophy. We all have patients who continue to have this, had

this, and continue to look like this. So we have subcutaneous lipoatrophy with apparent venomegaly. I always tell patients that their veins aren't getting bigger but the fat around it has decreased so the veins appear more prominent. Facial lipoatrophy being a big issue. And then on the other side of things, we have central lipohypertrophy. So we have in addition to the expansion of the visceral adipose tissue, lipomastia and "buffalo hump" and lipoma in other places, women can get breast enlargement from lipomastia as well.

[00:03:59] And initially it was thought that there was this redistribution, fat was going from the subcutaneous space into the visceral compartment. And the FRAM study led by Carl Grunfeld really showed that this was untrue. And so he recruited from a bunch of different sites around the country, men and women who are HIV positive some of them had lipoatrophy. And you can see here is LA positive in both the men and the women, and LA negative. And this is the visceral adipose tissue measurement, the controls are from the CARDIA study. And so what you'd expect is that if there was a redistribution of fat that the people, the men and the women who had lipoatrophy would have more visceral fat. So that there would be this reciprocal relationship. And what you see is that the lipoatrophy tends to be a little bit lower than those without lipoatrophy and you see the same thing for the women. So this really put to rest this idea of a fat redistribution syndrome.

[00:05:00] So what was the underlying pathophysiology? Now the lipoatrophy was a little bit easier to explain and this had to do with with the effect of finding analogs on mitochondrial function and particularly mitochondria in the fat. And so these medications in particular stavudine, to a lesser extent AZT inhibited DNA polymerase gamma. So you get this depletion of mitochondrial DNA, you get apoptisis of fat cells, and this would set up an inflammatory process. And when severe, stem cells left behind in the fat would also die and making it a really difficult problem to deal with. And so what we see now and we see this in our clinics all the time, is people who have been exposed to these drugs still have vestiges of these problems. Lipoatrophy goes away a little bit but not really.

[00:06:01] And we have people who continue to have facial lipoatrophy. Lots of people who have who have subcutaneous lipoatrophy to their legs and buttocks, that really doesn't change even though they might be off of thymidine analogs for 15 years now. And so this is seen in a study, CVD substudy, I work in the multicenter AIDS cohort study as some of you may know this is a study that's been going on since 1984. At four sites around the country and we have about half HIV infected, half HIV uninfected men who have sex with men, and we did a cardiovascular substudy. And we did measurements of visceral adipose tissue and subcutaneous adipose tissue relating these fat deposits to cardiovascular disease. This is just the data showing the difference between those living with HIV and those without HIV in this subcutaneous adipose tissue. And you can see at every BMI category, there's less subcutaneous fat in the HIV infected men compared to the uninfected men. So this is a description of this legacy effect. So even though the men are no longer on thymidine analogs, they still have have less subcutaneous fat and this fat that persists is a sick fat.

[00:07:22] And so I purposely was looking for a relatively recent reference and this is 2014, what this shows is biopsy samples of fat in people living with HIV. And this stain has to do with apoptosis, and this has to do with inflammation. This is TNF alpha. And so what you see is that this fat that's left behind, what fat there is, is an inflammatory fat. And so typically in your average obese person as the adipocytes hypertrophy, there's increased inflammation there and that's thought to mediate some of the effects of the relationship between obesity and Type 2 diabetes, or obesity and cardiovascular disease. Here there's less fat but it's still a very inflammatory fat. So it's this sick fat that is left behind, which can cause legacy problems for people who have been exposed to thymidine analogs in the past.

[00:08:19] So what about on the visceral fat? Also in 1998, the first descriptions of of increased visceral fat were made. And this is again from the same study that I showed you before the MACS cardiovascular substudy. And what you see is that looking between the HIV positive and HIV negative, those who are in the obese range there is really no difference in their visceral adipose tissue. But for those with normal weight or in the overweight category, the HIV infected men have higher visceral adipose tissue. Why this is really hasn't been known, 20 years later really isn't well known. So whereas with lipoatrophy, it's really a story of thymidine analogs, the effect on adipocyte apoptisis. From the increase in central fat, it's not really well described. It's not pinned on protease inhibitors as was initially described. Taking people off of protease inhibitors generally doesn't decrease the visceral fat.

[00:09:26] So there is a few hypotheses of why people may get this. One of them is an interesting one, so we know that another state that's related to expansion of visceral adipose tissue is Cushing's Syndrome, so hypercortisolemia. And so there is an enzyme called 11-beta HSD that locally makes cortisone into cortisol. And it turns out that people who have clinical lipodystrophy have higher expression of this 11-beta HSD, suggesting that they're more likely to make local cortisol. So whether or not that's the whole explanation is unclear but it may be one of them.

[00:10:09] Another potential cause here is abnormal growth hormone dynamics, and so there's been some nice work mostly done by Steve Grinspoon at Mass General over the years that has really established the growth hormone IGF1 axis as a major player in central fat accumulation in people living with HIV. And so what you see in the panel on the left is overnight growth hormone concentration. So growth hormone changes overnight and the best way to assess the growth hormone axis is to bring people into a research center and to test their blood every 20 minutes for growth hormone, so you can really look at the spikes of growth hormone. So what you see is that the people with clinical lipodystrophy have lower overnight growth hormone concentrations when you average things out, compared to the HIV infected without lipodystrophy or the controls. The other way of looking at this abnormal growth hormone axis is to try to stimulate the axis and one way to do this is with the growth hormone releasing hormone and arginine. And so what this shows you on the right, is the proportion of people who fail this stimulation test at various cut offs. So it's unclear in the endocrine world exactly

what's the best cutoff for these stimulation tests but the black bar is those with lipodystophy, and what you see is that compared to those without lipodystophy or controls, the failure rate no matter what cutoff you use is higher in those with lipodystrophy suggesting a relative growth hormone deficiency.

[00:11:50] And this growth hormone secretion is related to intra-abdominal fat. So the lower the growth hormone secretion, the more abdominal fat that people have. So this I'll talk about in a little bit. This opened the way to looking at the growth hormone and growth hormone releasing hormone analogs to treat central fat accumulation. But let's talk a little bit about the potential consequences of increased central fat. There are all kinds of associations in HIV and in the general population with this central fat accumulation and various health outcomes. So dyslipedemia, fatty liver disease, cognitive impairment, coronary plaque and that's the paper that I showed you from Frank Palella, health related quality of life. We've recently showed an association with frailty and actually mortality. And so the question is whether we can decrease visceral fat and improve some of these clinical outcomes, it is something that we still don't exactly know that answer.

[00:12:54] The other thing about about fat that's important to talk about is where some of these other depos might be. And so we talk about the central fat accumulation, but fat happens in so-called ectopic places. So in the pancreas, pancreatic fat can lead to decreased beta cell function and and decrease insulin secretion and can precipitate diabetes. In the muscle, fat within the muscle can decrease muscle performance. In the heart there's a close association between fat around the heart and around the arteries and fat within the heart, and heart function and endothelial function. And fat within the liver which is well characterized.

[00:13:42] So let's talk a little bit about fat within the muscle. This is a cross-section of two people. There's a 40 year old and a 70 year old you know nothing to do with HIV. So here's the muscle, there's the bone in the middle. And so what you see is that in the 70 year old, lots more fat in white, in the subcutaneous space. But if you look in the muscle, this darker area, you can see much more marbling of muscle in the older person. So in this, fat is not only between the muscle bundles but also within the muscle. And so not only is there lower muscle mass in the 70 year old, but there's lower muscle quality.

[00:14:24] And so we've been looking at this quite a bit in people living with HIV and this is an analysis that we did in the MACS, looking at thigh muscle attenuation. So you do a C.T. scan of someone's thigh and you can not only look to see how much muscle is there but by looking at how at the hounsfield unit of attenuation you can see the quality of that, and the lower the the hounsfield unit of attenuation the more fat there is in the muscle. And so what this shows you is then in blue, that line that's going pretty much straight across, is the HIV uninfected men. And so there's really not, in this age range, really not too much decrease in muscle quality. So the fat and the muscle stays the same. But in the HIV infected

men, you see in green, with increasing age there's decreasing attenuation means more fat in the muscle. And so we do see this quality defect in the HIV infected men.

[00:15:29] In the heart, we see a similar thing. And so as I mentioned before, so here is a heart with lots of fat in different places, and the fat can be either in the pericardium or in the epiardium or even in the myocardium. So myosteatosis, which is affecting heart function. So we've looked quite a bit at the epiccardial fat, which may have local factors these inflammatory factors which may change coronary endothelial function. And so we've shown in the MACS that this epicardial fat is increased in HIV infected men compared HIV negative. And then Giovanni Geraldi's group in Modena has shown that this epicardial fat is associated with coronary events, independent of other coronary risk factors. So this might be a major mechanism for coronary disease among HIV infected people.

[00:16:22] So we see this in the general population too. And some of these body composition changes, it's important to keep in mind happened with ageing. And so this idea of sarcopenic obesity where you have increased visceral fat, decreased subcutaneous lower fat, lower body fat with increased hepatic fat, and increased intramuscular fat, and more epicardial fat. And so we're seeing as we know this convergence of HIV and the ageing related effects and you see this compounded in body composition.

[00:16:59] And there is this interaction between the amount of fat people have and their skeletal muscle, so this is from the FRAM study where they did a whole body MRIs and they tried to look at at the association between the visceral fat, so how much fat you have in the abdomen, and the skeletal muscle fat. And so this is the tertiles of skeletal muscle fat. So this is the lowest tertile, this is medium, this is the most skeletal muscle volume. And then what you see is particularly in the low skeletal muscle tertile, increasing fat is associated with increasing mortality. And so it's really in this group that has this sarcopenic obesity where you see this mortality issue. So it's this convergence of sarcopenia and increased visceral fat that seems to be a particularly pernicious combination.

[00:17:59] So where are we in in 2018? One of the things that that is still not known is what are the unique contributors that increases visceral fat in HIV infected people? And so we have a convergence of epidemics, we have an obesity epidemic and we have with HIV a great number of people that are ageing with HIV. So we are trying to understand what's ageing and what's increased adipocity and what's HIV, has been really tough to to figure out.

[00:18:33] The other thing that is becoming increasingly characterized is this first two years after antiretroviral initiation, even in the modern antiretroviral era, is associated with very marked changes in body composition. And so this is a study from Patty Mallon early on in the HAART era, and what he did was look at body composition changes with people starting on antiretroviral therapy and most of them

were starting on a PI regimen plus d4T. And what it shows is an initial increase of CAF, central abdominal fat. LF is leg fat. And in the first 24 weeks, so first six months there's an increase in both leg fat and central abdominal fat. Central abdominal fat pretty much stays constant thereafter, but with the leg fat you see this decrease which is due to the d4T that we use.

[00:19:30] So what about the modern, this is that was you know 20 years ago what about where we are now? So this is a study that we published a couple of years ago. This is the last big ACTG trial, everyone was on TDF/FTC randomised to boosted darunavir, boosted atazanavir, or raltegravir. And we did in a subset of these patients, we did C.T. scans among other tests. And what you see here is that in these modern ART regimens, you see big increases in both visceral adipose tissue and subcutaneous adipose tissue in each of the regimens. And really no difference in this study, this smaller subset, by the type of regimen. Integrase versus P.I. But the increases in visceral fat are quite big, so about 30 percent or so.

[00:20:22] And so what about this central fat? How does this compare to what you would see in an HIV uninfected population? So we looked at this in comparison to this red line on the bottom is HIV uninfected people followed over an eight year period, and you see some modest increases in central fat, trunk fat. And we have the same thing for a total fat and subcutaneous fat as well. But you look at the HIV positives and the zero is when people are starting antiretroviral regimens and you see this initial big increase in their trunk fat, which keeps going and really very much outpaces what you would see in an HIV uninfected population. So what we're seeing with antiretroviral initiation really is quite abnormal. The associations of what leads to a greater increase in fat are just beginning to be worked out. One of the important things is that the higher the viral load and the lower the CD4 cell count prior to antiretroviral initiation is associated with greater increases in both visceral adipose tissue and subcutaneous adipose tissue. I didn't have a slide about this, but Grace McComsey my colleague at Case has also shown in a paper this year, that markers of gut permeability prior to antiretroviral initiation are also associated with this increase in fat. Suggesting that this leaky gut and the ensuing inflammation may also be playing a role in fat accumulation after antiretroviral therapy.

[00:22:00] So I had mentioned this idea of fat in the muscle. And so one of the things that we see with antiretroviral initiation is that lean mass increases and we think that's a good thing, people are getting better, their viral load is coming down, their CD4 cell count is going up, and if you look at their DEXA scans and their lean mass that's going up. But it turns out that the lean mass that is being gained is not sort of healthy lean mass, it's fatty lean mass. And so this is what this tells you. So in this study and this is from the raltegravir two boosted PI study, the ACTG study, where we analyzed the scans we didn't have the thigh slices, but we could measure the muscles that are in the abdomen. Including going through the abdominal cavity, like the rectus, and the psoas, and the spinalis. And what you see is this graph on the top, and these are the various sites. If you can't see the top one is the obliques, the rectus, psoas, spinalis. And if you look at the total muscle area you say 'all these muscles are increasing in size, oh antiretroviral therapy must be great for the muscles right?' But then you look at the lean muscle

area, so you're taking out the fat that's on the scan because it has lower density, and really there's no change in the lean muscle but if you look at the hounsfield unit, the density is actually going down suggesting that the muscle is becoming more fatty with antiretroviral initiation.

[00:23:39] And so there is increased muscle mass, yes, but it's fatty muscle with antiretroviral initiation. And what the consequences of that is something that remains to be seen. So we do get this fat increase with antiretroviral initiation. This is looking at a big study, the D:A:D, the cohort of cohorts mostly in Europe and what they did is they looked at the changes in body mass index with antiretroviral initiation in various strata. So people who started as underweight, normal, overweight, or obese. And what you see is that the obese group in this study, maybe increase a little bit in terms of their BMI. But if you look at the overweight, the normal weight, and particularly the underweight group, there are big increases in BMI. And in this underweight group you think, 'well is this a good thing or a bad thing? Is this a return to health phenomenon or is this something that's pathologic?' So that's something that still is unresolved. But even in the normal weight group you see pretty big increases in BMI by five years, about 1.38 kilograms per meter squared.

[00:24:55] And so they also ask the question, if these increases in weight are associated with bad outcomes? And the bad outcomes they were looking for are incident diabetes and cardiovascular disease. And so this is the cardiovascular disease events. So this is the null line here, so if this confidence interval overlaps the null line it means that it's not statistically significant. So overall they didn't see much of an association between the increases in BMI and cardiovascular events, but then they looked at each of these categories and clearly in the normal BMI group the weight change that you see with antiretroviral initiation is associated with increased cardiovascular events. So this suggests that this weight gain that you're seeing, at least in this normal group, isn't a return to health phenomenon. This is actually a bad thing in that it's associated with increased cardiovascular events and all the adjustment, I didn't show it you the circle on the end there for those third of the three lines is adjusted for traditional cardiovascular risk factors.

[00:26:04] So what about diabetes? So here you see overall there is an effect. The underweight group, there really is no effect but the confidence intervals are wide. But really in the normal weight group and the overweight group, this is where we see an increased risk of diabetes with the increased BMI in the first year after ART initiation. So this first year after ART initiation appears to be a critical time when a) there is weight gain and b) that the magnitude of that weight gain is associated with metabolic badness down the road.

[00:26:36] And the VA has shown a similar thing where they looked at weight gain during the first year after ART initiation. And they also looked at a similar one year period in people who are HIV negative and they looked at their risk of diabetes for a weight change in a year. And so you have people whose

weight remained stable, so that's the zero change group. And then as the weight increases, the risk of diabetes increases as well, and this is true in the HIV positive and HIV negative. But what you see which is sort of interesting, you notice that the scale on the y axis is the same between these two graphs, is that the slope for the HIV positives is steeper than the HIV negative suggesting that for the same increment of weight in the HIV positives the risk of developing diabetes is higher than in the HIV negative. So this added weight in the HIV positives means more than the HIV negatives.

[00:27:39] And we see these studies that I've talked about so far are sort of European or U.S. based, and just to show you this is really isn't a limited phenomenon that's limited to resource-rich settings. This is the PEARLS study which is done mostly in low and middle income countries, randomising to TDF versus AZT plus efavirenz. And what you see is that there's an increase in BMI in both of these arms and if you look at thigh circumference and hip circumference as well, an increase overall in both these arms with antiretroviral initiation. They looked at changes in inflammatory markers with antiretroviral initiation based on their BMI category at baseline, and they saw an interesting thing. I want to draw your attention to this CRP and CD14. So with CRP, we know that people that are underweight are also gaining weight, but that's associated with the decrease in CRP. And a tendency to decrease in soluble CD14 suggesting that this might be a good thing for them, but it's not for those who are overweight or obese. This increase in weight that you see is associated with a higher level of soluble CD14.

[00:29:00] So we've talked a little bit about antiretroviral initiation. So one question that comes up is are all ART regimens created equal in their weight gain? So we started looking at this a little bit more so Priya Bhagwat who's at UCLA, started looking at this in the larger group. I just showed you the body composition data for this study where people are randomized to either raltegravir, boosted darunavir, or boosted atazanavir, but this was a subset. This was the actual larger study, about 2300 people. And we did waist circumference measurements and hip circumference measurements as well as weight change. So this is the waist circumference change data in the larger group with antiretroviral initiation with each of these, so green is raltegravir, blue is boosted atazanavir, and red is boosted darunavir. And you can see in the graph on the left, which is the men, that there is an increase in waist circumference in all of these regimens, the slope of these lines is about the same. But in the women the slope is different and what's different? It's the green line which is raltegravir. So this is really the first study that says 'hey maybe there's something going on with the integrase inhibitors.' Integrase inhibitors are acting a little bit differently, not so much in men, but really in the women where there's a greater increasing waist circumference in the women.

[00:30:37] So Priya also looked at interactions by race and so on the left is black non-Hispanic. And then on the right is other races. And on the right you see that the lines are pretty much parallel. But again the magnitude of the increase for waist circumference is higher in that green line, the raltegravir, in the black non Hispanic group. So it looks like there's an interaction by race and an interaction by sex.

[00:31:08] So there's been a bunch of data that's come out in the last year and we'll be seeing much more at CROIS that has sort of substantiated these first findings. And so this was a study that Roger Bedimo did that was presented in his IDWeek presentation looking at the same kind of thing, big clinical cohort in Dallas. And so you can look at it with antiretroviral initiation with a P.I., within an NRTI, and an integrase inhibitor and you can see there's increases in BMI across the board. But the biggest increases are in the women, compared to the men. So the blue compared to the red, particularly with integrase inhibitors. And so this graph here on the right looks at the increase in BMI by racial group. So blacks, Hispanics, and non-Hispanic whites. And you can see particularly in the blacks, which is exactly what Priya had seen back in the ACTG data. So mostly in women, mostly in blacks.

[00:32:16] This was presented last month at the comorbidities workshop. This was a study looking at antiretroviral initiation in Brazil, and they looked at a bunch of different factors that may be associated with weight gain. And so this is one model, so they're adjusting for sex and adjusting for baseline weight, and year at ART initiation, and CD4 and viral load. And what I want to draw your attention to is the effect of of integrase inhibitors versus NRTI is associated with about a 4 kilo higher weight increase compared to NRTI. Okay so the effect that you see with NRTIs, if we're talking about kilos, is about a 4 kilo difference and that's on the order of what you see with with atypical antipsychotics. So we know that atypical antipsychotics coming out about 15, 20 years ago really very important in terms of psychiatric care, associated with weight gain. Weight gain that is related to diabetes and the magnitude of that increase is somewhere in the 3 to 5 kilo range.

[00:33:28] So this is the largest study so far, by far, looking at NA-ACCORD which is a cohort of cohorts in the US, and Jordan Lake presented this at the comorbidities workshop and she shared these slides with me. And so you can see these numbers, about 21000 people initiating antiretroviral therapy in NA-ACCORD. And you can see the demographics here. And looking here at the integrase inhibitor, still relatively few people initiating on integrase inhibitors in the whole NA-ACCORD data. You know that will change in the next in the next few years as the dataset becomes more mature. And the other thing to notice here is that when you look at the integrase inhibitors that are used, you see raltegravir, which is obviously you know the first integrase inhibitor you're going to have most people who are initiated on it. You have elvitegravir and dolutegravir, but relatively small numbers. You don't see any bictegravir, it's too new to really see it in the cohort. And you can see overall that it's really 2 percent of the initiators are on dolutegravir. And so that really doesn't reflect the practice now, so we need to see these data further on in the future.

[00:34:41] But what do the data show? And so what you see is that the y axis is the predicted weight in kilograms, and so what you see is that there's increase in kilograms with antiretroviral initiation as we've seen before. But the greatest weight gain that seen is with the integrase inhibitors, next the PIs, and finally the NRTIs. And so what about which integrase inhibitor might be the biggest problem? And so here is raltegravir and so you can see clear separation. Elvitegravir it looks like it starts to go down after

a couple of years, but keep in mind how wide these confidence intervals are. We just have a few people who are observed that far out, so this is pretty unstable here. So it may or may not be going down. And with dolutegravor. So in this study couldn't really discern which of the integrase inhibitors might have a bigger effect.

[00:35:50] So one of the things with integrase inhibitors is that they reduce viral load very quickly. And so one of the hypotheses is that with antiretroviral initiation, maybe that has something to do with the weight gain that you see, is the fact that they're so effective. But you actually also see this problem with people who are suppressive regimens, switching to integrase inhibitors. And so this is a study that John Koethe's group did at Vanderbilt, looking at people who stayed on a regimen of efavirnez, TDF/FTC, or switched to an integrase inhibitor and you see over this time period of about a year and a half that there's this increase in weight in those who switched to an integrase inhibitor, that you don't see when you look at people who switch to preotease inhibitor. And then trying to figure out, well which of the regimens seemed to be driving the effect? And in John's data it was the dolutegravir/abacavir/3TC that seemed to have the biggest effect, this graph on the lower right.

[00:36:52] So there's a lot of questions that we have about integrase inhibitors and fat. And this is as I mentioned we're just starting to see this data, we'll see a lot more data CROIS we'll see a lot more data after this because there are a lot of questions. So what are the mechanisms underlying it? Generally you think with with fat increase it is a central effect on feeding, that it causes decrease in satiety so people eat more. Could be an effect on energy expenditure where there's less energy expenditure or it could be an effect on the fat causing increased differentiation and proliferation of adipocytes. So trying to figure out exactly what the mechanism is unclear. Why it seems to impact women and non-whites to a greater extent is something that we need to know. What are the clinical consequences? So we know that it's somewhere around three to five kilo increase in fat, the integrase inhibitor effect. But what we don't know is are different depos affected differently. Is it more of a visceral adipose tissue or subcutaneous adipose tissue? What about the effects on atopic fat? What about the effects on epicardial fat, on intramuscular fat, on liver fat, on pancreas fat?

[00:38:11] So all of this needs to be investigated and importantly what do we do clinically? We use integrase inhibitors a lot, they're great drugs. Do certain people do we switch back. Do we switch from integrase back to NRTIs? Do we avoid in certain people integrase inhibitors with antiretroviral initiation if there are other options? Should we be giving concomitant medications like metformin, which is used now in combination with atypical antipsychotics to decrease the metabolic effects? I threw in GLP-1 receptor analog, should we be trying to combine these drugs to try to mitigate the effect that we see with integrase inhibitors and fat? So I think we're going to be seeing a lot of data about this coming out and there are a lot of questions.

[00:39:03] So what do we do from a clinical standpoint? And so I draw your attention to this paper that Jordan Lake was the first author of, a bunch of us got together to talk about about how to manage these issues of lipohypertrophy and obesity in people living with HIV. So the cornerstone of treatment with both obesity and lipohypertrophy is changes in lifestyle. And so this idea of looking at calories in and calories out, and that's critically important. I only have one slide, in the interest of time, but we get a lot of calories from many sources throughout the day. We're given many more calories than we actually need when we go out to out to eat for example, this is what we get when we go to fast food. This is what we really need to be a serving size. And so we are getting more calories than we need and we are of course having less activity than we really should. So this is really the cornerstone of our treatment.

[00:40:08] And we know that the balance of of decreasing energy coming in and increasing energy going out is important, and important in terms of their risk of diabetes where 150 minutes a week of exercise and caloric restriction with a goal of 7 percent weight loss is associated with about a 60 percent decrease in the incidence of diabetes. And so this is the graph here, this is the placebo here in blue, lifestyle red, and you see over this five year period people with pre-diabetes who get this lifestyle modification have about a 60 percent decrease in diabetes risk. And we know at least in the general population that this 7 percent weight loss is associated with decreases in inflammation. And so this is about cutting calories in by about 500 calories, leading to this 7 percent weight loss and about a a 50 percent reduction in TNF-alpha, about a 30 percent reduction in CRP. So it can definitely at least in the general population, this mild amount of weight loss can be important in terms of levels of systemic inflammation.

[00:41:29] And we know that a similar program to the DPP program that I just showed you works in HIV infected people. So this is a study that was done by Steve Grinspoon's group, Katie Fitch there looked at how to control, attention control, and a lifestyle modification modeled after the DPP program that I just showed you, showing significant reductions in in blood pressure and in waist circumference in those people who did lifestyle measures.

[00:41:57] So what about adding drugs? What about adding drugs to help with the weight loss to help with the central fat accumulation? So this is where we need to be weighing the potential benefits of these drugs against the potential risks and then of course the costs that are really quite real for patients. And part of the problem here, and this is true for lipohypertrophy as I'll talk about and also for the obesity drugs, is that these are really short term trials. And so the long term risks and the long term benefits really haven't been figured out yet. We generally think that decreasing visceral fat or decreasing obesity is probably good for people's health in the long term. And decreasing lipids, decreasing risk of diabetes, decreasing cardiovascular disease, potentially but really they don't know that from the trials. The other thing is that the long term risks haven't really been figured out and for many people there's big out-of-pocket costs there. And so when we think about these drugs whose main goal is to decrease fat, the calculus changes a little bit. And we want a drug that is has very few risks and that ideally is

cheap, but that's really difficult to achieve something that is going to give you sustained benefits and perhaps long term benefits.

[00:43:27] So one of the first drugs, talking about central fat accumulation that was investigated was metformin. And so Steve Grinspoon's group, so Colleen Hadigan was the first author of this early study looking at metformin at a relatively low dose so 500 bid. Showing that metformin compared to placebo could improve insulin resistance, in this case the insulin area under the curve, and could decrease waist circumference. So other studies have shown this, it is a relatively modest effect, but it does work. The area that has been developed the most is looking at the growth hormone axis and I showed you the growth hormone axis abnormalities in people with lipodystophy. And just to remind you a little bit about what growth hormones access looks like, so growth hormone releasing hormone is released by the hypothalamus to act on the pituitary to release growth hormone, which acts on the liver to release IGF1 which is really the business hormone of the growth hormone axis. And there are some other regulators of this axis including somatostatin which is also released by the hypothalamus, and the stomach releases ghrelin which is a positive regulator.

[00:44:40] So if you look at someone here who has relatively low growth hormone secretion. So I was telling you about this every 20 minute test looking at growth hormone curves, so which is sort of the gold standard way of looking at growth growth hormone secretion. You can look to see that overnight there is increases in growth hormone periodically, so there are these pulses, but after you add in growth hormone releasing hormone these pulses increase in amplitude and a little bit in frequency as well. And so this provides some rationale to try to use growth hormone releasing hormone or growth hormone releasing hormone analogs to try to bring back the pulsatility of the GH axis.

[00:45:27] And so looking at tesamorelin or GHRH, tesamorelin is a growth hormone releasing hormone analog, or GHRH itself. What happens here is instead of giving GH, which is going to cause IGF1 release and potentially could cause negative side effects by not preserving the feedback mechanism, when you're giving tesamorelin or GHRH you're preserving that feedback mechanism. So IGF1 will decrease the amount of GH that the pituitary can make in response to the tesamorelin. So it's an added safety measure by targeting the axis at the hypothalamus rather than at the level of the pituitary.

[00:46:17] So this is the study, tesamorelin is an approved drug for central fat accumulation, so this is the trial that was the licensing and registration trial for this, where people with central fat accumulation were randomised two to one treatment versus placebo and then after 26 weeks they were randomised. So the placebo people got on treatment and the treatment people were randomised to either get treatment for another 26 weeks or placebo. And actually, Steve Grinspoon designed this which was really pretty clever actually, because people wanted to be on the treatment and so they wanted to stick around. So even if they were randomised to placebo, they just had to stick around and they would get

eventually 26 weeks of the drug. So this is the biggest problem in in these kinds of trials, including obesity trials, that people get randomised and then if it's not working for them, they leave the trial. And so if you look at the completion rate of some of these obesity trials it's like 55. 60 percent. And the people who are leaving the study are informative dropouts. These are people who aren't seeing any benefit. So it's really difficult to interpret some of these data. So when you see an obesity trial always look to see at the end of the trial how many people were left and how informative those people were who left, were these people who were not losing weight?

[00:47:45] So the bottom line here, this is the main results, that those people who were randomised to the tesamorelin after 26 weeks had about a 15 percent decrease in VAT compared to placebo. And this is the other study whereas about a 12 percent decrease and no effect really in placebo, and importantly no effect on subcutaneous fat so this seemed to be a relatively targeted medication for visceral adipose tissue. The problem is in the extension. So in the extension, as I told you that people who are randomised to the treatment half of them were randomised to placebo in that second period, and in that second period those who were randomised to placebo pretty much gained back all their visceral fat. And so you need to stay on the drug to continue those benefits. And so tesamorelin has been out for for you know six or seven years now, but there's still a lot of unresolved issues. So really who is the optimal patient? How do you say OK this patient should merit a trial of tesamorelin? Generally I see a lot of patients who are referred to me as an endocrinologist from our HIV clinic and these are people who are interested in decreasing their belly fat. I don't really go out there, if I'm seeing someone for their osteoporosis and they have increased belly fat, I don't say 'Oh have you thought about tesamorelin?' So how long should it be given?

[00:49:15] So we know that once you stop it the visceral adipose tissue comes back, so that's a big question. How long should it be given? And in the trials there was no additional dietary or lifestyle, so can you use this drug to sort of jumpstart a lifestyle plan to decrease visceral fat through non-pharmacologic measures? And then as I mentioned before, this calculus of risks and benefits. So long term risks we don't know. So higher levels of IGF1 theoretically are associated with malignancy. We don't really have long term data because the longest time people have been observed on this so far has been 52 weeks. So we really don't know the long term effects. And benefits we think visceral adipose tissue decreasing that is a good thing, but does it decrease cardiovascular disease? Does it decrease the risk of diabetes? Unclear. And then of course do any benefits do they justify the costs? This is an expensive medication and so is it worth? It is it worth it for the patient for their out-of-pocket costs is it worth it for the healthcare system?

[00:50:25] So let's switch gears and talk a little bit about about the pharmacologic treatment of obesity because in the last five or six years there have been a bunch of medications that have come out. And this is a table from Jordan's paper in CID, so there really are five FDA approved medications for obesity. So the first one is orlistat, that really isn't used very much. So this is Alli, so this is the one that's the

pancreatic gastric lipase inhibitor, it's associated with faecal incontinence. It works a little bit, but not really. So it's over-the-counter now, people don't use it a lot. There have been some studies where HIV infected people have lost virologically control because of absorption issues. So my feeling is to avoid it. Doesn't work very well. Bad side effects. You have this potential of loss of virologic control. So the drugs that I have used are combination drugs so phentermine-topiramate. So phentermine as you know is one of the drugs in FenFen, it was taken off the market. Or fenfluramine was taken off the market because of valvular issues and pulmonary hypertension. But phentermine increases energy expenditure and in combination with topiramate, is a pretty effective way of losing weight. So there are some side effects to it. So insomnia, dry mouth, constipation, paresthesia, dizziness, and dysgeusia, also cognitive effects with the topiramate. So you have to watch out. There is, looking at drug-drug interactions, so topiramate is an inducer of CYP3A4. But the clinical relevance, it's a mild inducer so there's probably not too much clinical relevance there. Lorcaserin is another one and so this works on the serotonin system and the side effects are headache, nausea, dry mouth, dizziness, and fatigue, and constipation. There are some issues you have to look to see what other medications they're taking to be sure, especially psych medications. The fourth one is a combination of naltrexone and bupropion. And so bupropion is an antidepressant that is used quite a bit. Naltrexone of course is an opioid antagonist, but in combination is a pretty potent way for people to lose weight. And you know these drugs are in a single tablet regimen but they can be split apart, and actually given for less of a price. So if you have a patient that's already on bupropion perhaps and they're interested in losing weight, adding naltrexone may be a good thing. And then the last one is a diabetes medication, so liraglutide. A higher dose in diabetes, liraglutide the trade name is victoza, can decrease weight in patients with diabetes. And patients without diabetes, it's an approved drug under the trade name of saxenda, at a higher dosage 3.3 milligrams rather than 1.8 milligrams. So some associations with nausea, vomiting, and pancreatitis but it does have some effect on losing weight.

[00:53:40] And if you looked at the magnitude of the weight loss here, this is the effect of lifestyle somewhere between 3 and 8 percent. So the combination here is around 10 percent in combinations of pharmacology and lifestyle, but really the big changes in weight are related to surgeries. And so we really have three surgeries that we do now. Adjustable gastric band is something that was in vogue about 15 years ago. It doesn't work too well and people are sort of moving away from it. And Roux-en-Y is both a restrictive and a malabsorption procedure where the stomach is transected and you make a small stomach pouch. You have the intestine is transected here and this limb is brought up, and so you have a malabsorptive of state as well. And this is associated with big decreases in weight. Big for patients with diabetes who are obese who get this, there's a very high remission rate of diabetes but there are some issues with vitamin deficiencies. We see in clinic, hypoglycemia related to Roux-en-Y gastric bypass. The other more mild disease which is really just a restrictive disease, is the vertical sleeve gastrectomy which is associated with a little bit less weight loss but this is the one I generally recommend to my HIV infected patients because I'm always a little bit worried with this malabsorptive state with Roux-en-Y that is going to affect antiretroviral absorption. There have been a bunch of, as far as the studies of this, mostly at the case report level or multiple cases at a single center, and most of them really show that the safety is quite good for either of these procedures either Roux-en-Y or vertical sleeve gastrectomy in terms of HIV control.

[00:55:40] So in conclusion, so body fat changes have been a major issue among people living with HIV really since the early HAART era. These legacy effects of ART on fat may impact current health. So the legacy effects of thymidine analogs. Central lipohypertrophy continues to be an issue and overlaps with obesity. So ectopic fat. So we talked about ectopic fat in the heart, ectopic fat in, the muscle in the pancreas, and in the liver have major effects on the organ function. And keeping an eye on this integrase inhibitor question is going to be important going forward and trying to address some of these questions that have been raised. Lifestyle changes are really critical in the management of lipohypertrophy and obesity. And we need to weigh the risks, benefits, and costs of these pharmacologic approaches and also talk to your patients about it. Always have a frank discussion about what we know, and what we don't know with my patients when we're considering these drugs. Thanks for your attention.

[End]