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Todd T. Brown, MD, PhD Diabetes risk, screening, and monitoring in people with HIV

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A publication of

The Center for AIDS Information & Advocacy, a program of **Legacy Community Health Services** P.O. Box 66308 • Houston, TX 77266-6308



Research Initiative / Treatment Action!

A publication of THE CENTER FOR AIDS INFORMATION & ADVOCACY

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Perspectives



By Mark Mascolini

Abstract: Diabetes prevalence continues to climb at an alarming pace across the world. Although HIV populations are no exception to this trend, diabetes prevalence varies 10-fold across studies of HIV cohorts because of differences in their composition and in diabetes definitions applied. Two of three studies that compared diabetes prevalence in people with and without HIV found higher rates in the HIV group. Among people with HIV infection, diabetes incidence is higher in US cohorts than in other groups, probably because of higher risk factor rates in the US groups. Though diabetes incidence was higher with than without HIV in earlier studies—when people were taking more toxic antiretroviral regimens-the largest and latest comparisons found lower diabetes incidence with HIV than without HIV.

Diabetes history reads like a roster of euphoniously named heroes. Everyone knows Banting and Best, who found that insulin regulates blood sugar. But who remembers Mering and Minkowski, or Sharpey-Schafer, or Aretaeus of Cappodocia? Not to mention the team of Langerhans and Languesse. Many an endocrinologist can tell you about Paul Langerhans, father of the eponymous pancreatic islets. But how many know G.E. Languesse named those islets (**Figure 1**)? And we can thank Sharpey-Schafer (Sir Edward Albert) for proposing the term *insulin* (after the Latin for *island*)¹ rather than *Langerhansin* (and the consequent *Langerhansinemia*).

If quizzed on who first described diabetes-or nearly any classical disease-you're safe to credit the ancient Egyptians. That's probably not because primeval Nile valley denizens had such an acute appreciation of diverse debilities, but because they kept heaps of hieroglyphic charts. Pritzker School of Medicine dean Kenneth Polonsky notes that disease-conscious Egyptians first recorded diabetes around 1500 BCE, pinpointing two key traits-prodigious urination and weight loss.¹ In the second century CE Greek healer Aretaeus minted the term diabetes mellitus,* acknowledging the sweet taste of a diabetic's urine. Mellitus means "honey sweet," but we do not know if Aretaeus personally gathered evidence of this saccharine signal. Diabetes comes from the Greek word for siphon, a possible nod to the diabetic's unquenchable thirst.3





Figure 1. French histologist G.E. Languesse named islets of Langerhans, which secrete insulin, for German pathologist Paul Langerhans, who discovered them but modestly dubbed them *Zellhaufen*, or "cell heaps."² (Pancreas and islets of Langerhans from Servier PowerPoint image bank, *http://servier.com/Powerpoint-image-bank*. Paul Langerhans from Wikipedia Commons.)

More than 1600 years elapsed after these Aretaean observations before someone—an English physician called Matthew Dobson—got the idea to measure glucose in urine of diabetics and confirmed lofty values.¹ In 1889 Mering and Minkowski (Austrians Joseph von and Oskar) ablated the pancreas from dogs, who promptly died of diabetes, and thereby showed that the organ plays a critical role in ruling glucose.¹

But how? Sharpey-Schafer, an English physiologist, hypothesized (and named) the pancreatic chemical insulin in 1910.¹ Only 11 years later Frederick Banting and Charles Best *reversed* diabetes induced in dogs by infusing pancreatic islet cells from healthy dogs, and their colleague James Collip purified the hormone insulin. The Nobel committee bestowed its esteemed prize on Banting and his boss John Macleod but passed

*Aretaeus was no lightweight. He published two four-volume tomes, one called *On the Causes and Indications of Acute and Chronic Diseases*, the other On the Treatment of Acute and Chronic Diseases, wherein he described not only diabetes mellitus, but also pleurisy, diphtheria, tetanus, pneumonia, asthma, epilepsy, and how to tell spinal from cerebral paralysis.³

up Collip and Best.⁴ Insulin became the first hormone ever cloned then massively produced for treatment via recombinant DNA technology,¹ the first chapter in a biotech revolution that has saved countless lives.

Global and US diabetes numbers grow

Diabetes mellitus shares three features with HIV infection. (1) Before research identified effective therapies, both diseases remained almost universally and painfully—fatal. (2) Once solid benchwork nailed down the pathogenic basics of each disease, brisk development of practical treatment turned both into manageable chronic diseases. (3) Neither can be cured. Despite diverse effective remedies for diabetes, Kenneth Polonsky argues that, "if one views diabetes from a public health and overall societal standpoint, little progress has been made toward conquering the disease during the past 200 years," largely because about 90% of cases today result from a global obesity epidemic.¹

Polonsky concludes that diabetes has become "one of the most common and most serious medical conditions humankind has had to face."1 To be sure, the global burden of 35 million cases of HIV infection pales beside the 387 million with diabetes.⁵ The International Diabetes Federation projects that diabetes prevalence will climb to 592 million by 2035 and notes that every

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country in the world records a rising tally of residents with type 2 diabetes.⁵

The American Diabetes Association figures that 29.1 million people in the United States had diabetes in 2012, or 9.3% of the population.⁶Those numbers rose from 25.8 million and 8.3% in 2010. Centers for Disease Control and Prevention (CDC) number crunchers reckon that diabetes prevalence in the country will double from 2005 to 2050.⁷ Parsing recent trends, Polonsky figures that 1 in 3 US adults could have diabetes by 2050.¹ The ADA estimates that 86 million US residents 20 or older had prediabetes (blood glucose 100 to 125 mg/dL) in 2012, up from 79 million 2 years earlier.⁶

Diabetes prevalence 3% to 14% with treated HIV

Research pegs diabetes prevalence in Western HIV populations at anywhere from an elfin 2.6% to a flush 14%,⁸⁻¹⁵ compared with the US general population estimate of 9%.⁶ This wide range should spark no surprise since the HIV studies varied in diabetes definitions, populations assessed, their diabetes risk factors, and their antiretroviral treatment status. The US estimate of 9% includes about 8 million people with undiagnosed diabetes, while the HIV calculations include only diagnosed people.

Table 1. Diabetes or severe hyperglycemia prevalence in Western HIV populations

Author	Year(s)	Site(s)	n	Age*, M/F (%)	Diabetes risks	Prevalence ⁺
Kilby ⁸	1988-1995	Birmingham, Alabama	1392	~44, 80/20	11 of 25 with high glucose black, 10 of 25 taking megestrol acetate, proportion on ART not reported	Glucose ≥250 mg/dL 1.8%
El-Sadr ⁹	1999-2002	US	419	M 38.2, 79/21	60% black, 10% Hispanic, BMI 24.2, antiretroviral naive	2.6%
Brown ¹⁰	1999-2003	US, MACS	568	M 46, 100/0	15% nonwhite, BMI 25, 72% on ART	14% on ART; 7% not on ART



Table 1. Diabetes or severe hyperglycemia prevalence in Western HIV populations (continued)

Author	Year(s)	Site(s)	n	Age*, M/F (%)	Diabetes risks	Prevalence ⁺
Polsky ¹¹	2002-2006	Bronx, New York	222	M 50, 47/53	61% black, 27% Hispanic, 37% overweight, 24% obese, 79% on ART, 58% HCV	5.4%
Savès ¹²	1999	France, APROCO	614	63% >34, 80/20	100% on PI therapy, 64% on d4T, 32% on ZVD, 29% on ddI, race not reported	5.7% (28 of 493 with glucose data)
De Wit ¹³	1999-2005	Europe, US, Australia, Argentina, DAD Study	33,389	M 38, 74/26	13% nonwhite, BMI 23.0, 73% on ART, 58% on PI	2.85%
Calza ¹⁴	2009	Bologna	755	37 w/o DM, 48 w DM, 66/34	3% nonwhite, BMI 23.1 w/o DM, 26.5 w DM, 87% on ART, 30% HCV	4.5%
Galli ¹⁵	2008	Milan	4249	M 45.7, 76/24	BMI 23.2, 29.6% overweight or obese, 91.5% on ART, 33% HCV	4.1%

* M, median; no M, mean.

† Diabetes mellitus defined (by reference number): 8, severe hyperglycemia defined as ≥ 250 mg/dL or antidiabetic medication; 9, history of diabetes mellitus; 10, fasting glucose ≥ 126 mg/dL, self-reported diabetes diagnosis, self-reported use of antidiabetic medication; 11, fasting glucose ≥ 126 mg/dL, 120-min glucose ≥ 200 mg/dL during OGTT, or antidiabetic medication; 12, fasting blood glucose ≥ 126 mg/dL, OGTT ≥ 200 mg/dL;
13, confirmed fasting blood glucose ≥ 126 mg/dL, physician report plus antidiabetic medication; 14, single fasting blood glucose ≥ 126 mg/dL, random blood glucose ≥ 200 mg/dL, antidiabetic medication; 15, fasting blood glucose ≥ 126 mg/dL, history of diabetes mellitus, antidiabetic medication.

ART, antiretroviral therapy; BMI, body mass index (kg/m²); d4T, stavudine; ddI, didanosine; DM, diabetes mellitus; MACS, Multicenter AIDS Cohort Study; M/F, proportions male/female; OGTT, oral glucose tolerance test; PI, protease inhibitor; w, with; w/o, without; ZVD, zidovudine.

The first report of high blood glucose in people with HIV charted proportions of patients with extremely high glucose-at or above 250 mg/dL, that is, twice the diabetes diagnosis cutoff of 126 mg/dL-in the 8 years before combination antiretroviral therapy (cART) arrived.8 This review from the University of Alabama at Birmingham does not say how many people were taking antiretrovirals, though most probably were since the study period began in 1988. But the study period ended in 1995, just before the cART era. Twenty-five people, almost 2%, had sky-high glucose (Table 1). Eleven of those 25 were black, and 10 were taking megestrol acetate (Megace), a synthetic progesterone then prescribed to stimulate appetite in people with HIV but now rarely used by HIV-positive people. The researchers did not report how many people met the 126-mg/dL cutoff.

In a 419-person antiretroviral-naive US cohort studied from 1999 through 2002, diabetes prevalence measured only 2.6%,⁹ not much more than the ultrahigh glucose prevalence in the Alabama study.⁸ This 1999-2002 study group had two notable high-glucose risk factors—60% were black and 10% Hispanic, and average body mass index approached the overweight threshold at 24.2 kg/ m². But this study probably underestimated diabetes prevalence because it used a loose definition—diabetes reported in patients' medical records.

Defined more rigorously (see footnote to **Table 1**), diabetes affected 3% to 6% of HIV cohorts in the Bronx, New York,¹¹ in France,¹² across Europe, the US, Australia, and Argentina,¹³ and in the Bologna¹⁴ and Milan¹⁵ regions of Italy. Almost all of these people were taking cART, high proportions were men, most were white, and most were not overweight or obese (**Table 1**). The Bronx group is an exception to these generalizations.¹¹ More than three quarters in these people were taking cART, but 88% were black or Hispanic, 53% were women, 61% were overweight or obese, and 58% had HCV infection, an established diabetes risk factor.

Another US analysis involved 568 HIV-positive men and 718 HIV-negative but at-risk men in the Multicenter AIDS Cohort Study (MACS) seen from 1999 through 2003 in four cities.¹⁰ Only 15% were nonwhite, and almost three quarters were taking cART (**Table 1**). Median body mass index in HIV-positive men measured 25 kg/m²—at the overweight threshold—regardless of cART status. Prevalence of diabetes (defined as fasting glucose \geq 126 mg/dL, self-reported diabetes diagnosis, or self-reported use of antidiabetic medication) stood at 5% in HIV-negative men, 7% in HIV-positive men not on cART, and 14% in HIV-positive men on cART.

Why did HIV-positive MACS men shoulder a higher diabetes burden than other US and European populations-a burden more in line with estimated diabetes prevalence in the general US population? The MACS analysis cannot be compared with the early University of Alabama study, which recorded prevalence of blood glucose at or above 250 mg/dL rather than the diabetes cutoff of 126 mg/dL.8 Diabetes prevalence may be higher in MACS than in the antiretroviral-naive US group⁹ because that study did not actually measure fasting blood glucose and so probably underestimated the true diabetes rate. Even so, blacks and Hispanicswith their higher diabetes risk than whites-made up a much greater proportion of the naive cohort (70%) than the MACS cohort (15%). And even the naive HIVpositive MACS contingent¹⁰ had more than a twice higher diabetes rate than the naive cohort.9

Substantially higher BMI could contribute to greater diabetes prevalence in MACS men¹⁰ (25 kg/m²) than in the largely European DAD Study (23.0 kg/m²)¹³ and the three other European groups (23.1 and 23.2 kg/m² in the Italian groups,^{14,15}; in France ranging from 22.5 kg/ m² in people with no sign of lipodystrophy to 24.1 kg/ m² in people with isolated fat accumulation¹²). Diabetes definitions and antiretroviral treatment rates were similar in MACS and the DAD and European studies. MACS included a 5-fold higher proportion of nonwhites (15%)¹⁰ than the Bologna study (3%)¹⁴ but a similar proportion to the DAD study (13%);¹³ the French and Milan studies did not report race. MACS men were almost a decade older than the DAD¹³ or Bologna¹⁴ groups but similar in





age to the Milan group.¹⁵ One third in each of the Italian groups had HCV infection. But the MACS investigators and the other studies did not report HCV status.

Why diabetes prevalence stood so much higher in MACS men¹⁰ than in Bronx men and women¹¹ is tougher to construe. The groups had similar proportions taking antiretrovirals, but the Bronx cohort had loftier rates of other risk factor that might have led to a higher diabetes prevalence—somewhat older age, higher body mass index, a much higher proportion of blacks and Hispanics, plus a lofty HCV prevalence (**Table 1**). The different diabetes rates could reflect a different diabetes definition in the Bronx study (see **Table 1** footnote) and the much smaller cohort.

Regardless of variables that may explain differing diabetes rates in these study group,⁸⁻¹⁵ how do these HIV cohorts compare with selected control groups in diabetes prevalence? Three of these eight diabetes studies compared prevalence in HIV-positive people with the rate in an HIV-negative control group. Two of



them found a higher diabetes rate in the HIV group 10,15 and one did not. 11

The MACS study of 568 HIV-positive men and 710 HIV-negative men seen at the same four US centers recorded lower diabetes prevalence in HIV-negative men (5%) than in HIV-positive men not taking antiretrovirals (7%) or HIV-positive men taking antiretrovirals (14%).¹⁰ After adjustment for age and body mass index, HIV-positive men not on treatment had more than a twice higher prevalence than HIV-negative men (prevalence ratio 2.21, 95% confidence interval [CI] 1.12 to 4.38), and HIV-positive men on treatment had more than a 4-fold higher diabetes rate (prevalence ratio 4.64, 95% CI 3.30 to 7.10) (**Figure 2**).

The study of 4249 HIV-positive people in Milan compared them with 9148 healthy controls from 15 regions around Italy.¹⁵ Prevalence in the HIV group stood at 4.1%, compared with 2.5% in healthy controls, a highly significant difference (P < 0.0001). Statistical analysis adjusted for age, gender, BMI, triglycerides,

Figure 2. Compared with HIV-negative control groups, HIV-positive men in the Multicenter AIDS Cohort Study (MACS) had higher rates of diabetes mellitus than HIV-negative MACS men regardless of antiretroviral use10 (prevalence ratios adjusted for age and BMI), and Italian men and women with HIV had higher odds of diabetes than men and women in the general population¹⁵ (odds ratio adjusted for age, gender, BMI, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol). A third study (discussed in the text)¹¹ found similar diabetes prevalence in Bronx adults with and without HIV.

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total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol determined that people with HIV had more than 50% higher odds of diabetes (adjusted odds ratio 1.55, 95% CI 1.02 to 2.31, P = 0.0035) (**Figure 2**).

A comparison of 222 HIV-positive people and 155 HIV-negative people in two Bronx cohorts charted diabetes prevalence of 5% in the HIV group and 8% in the no-HIV group.¹¹ At the same time, the combined rate of impaired fasting glucose plus impaired glucose tolerance was almost twice higher in the HIV group than in the comparison group: 26% versus 14%. High rates of diabetes risk factors in both the HIV-positive group and the HIV-negative group (nonwhite race, overweight and obesity, HCV positivity) could explain why diabetes prevalence did not differ by HIV status in this study.

None of the three studies comparing diabetes prevalence by HIV status took place within the past 6 years.^{10,11,15} Diabetes incidence comparisons by HIV status, reviewed below, indicate that diabetes incidence has become lower in HIV-positive than negative people in recent years.

Incidence above 1 per 100 person-years in US HIV+

The International Diabetes Federation,⁵ the American Diabetes Association (ADA),⁶ and the CDC⁷ agree that diabetes prevalence keeps climbing at a heady pace around the world, and that can mean only one thing: Incidence—the new diagnosis rate—far outstrips mortality of people already afflicted with diabetes.

Headcounters reporting for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) say clinicians diagnosed 1.7 million new diabetes cases in the United States in 2012.¹⁶ In contrast, about 50,000 US residents get infected with HIV every year—3% of the diabetes rate. Overall US diabetes incidence stood at 0.78 per 100 people but was higher in people 45 to 64 (1.20 per 100) and people 65 or older (1.15 per 100). And those rates do not reflect untold cases of undiagnosed diabetes.

In 11 studies of people with HIV infection,^{10,11,13,17-24} diabetes incidence ranged from 0.37 per 100 person-years (p-y) in Denmark²⁰ and 0.42 per 100 p-y in the largely European DAD study¹⁹ to 4.7 per 100 p-y in a 10-yearold MACS survey¹⁰ (**Table 2**).* This 10-fold range reflects cohort differences in age, diabetes risk factors (especially race and weight), and diabetes definition. The study with the longest follow-up, a 10-year audit from France, charted an overall diabetes prevalence of 1.41 per 100 person-years.²² But that rate plunged from a high of about 2.5 per 100 p-y in 1999-2000, when many people were taking toxic antiretrovirals like indinavir, stavudine, and didanosine, to a low of about 0.5 per 100 p-y in 2005-2006 and 2007-2009.

Except for the nationwide French study,²² diabetes incidence lay below 1 per 100 p-y in European studies13,19-21 and above 1 per 100 p-y in US studies (Table 2).^{10,17,18,23,24} (In another 1149-person US study that did not lend itself well to the comparisons made here, diabetes incidence measured 3.5 per 100-personyears.²⁵ More than two thirds in this Baltimore cohort were black.) The European cohorts included more than 42,000 HIV-positive people,^{13,19-21} compared with about 13,000 in the cited US studies. From 7% of 15% of the three big European cohorts were nonwhite,13,19-21 as in the US MACS study.¹⁰ But in the other US studies more than half were black and many others Hispanic-groups with a higher diabetes risk than whites. Body mass index centered around a healthy 23 kg/m² in the European studies,^{13,19-21} compared with median BMIs usually in the overweight range in the US studies.

* This analysis includes two DAD cohort studies, which primarily include Europeans. The later DAD analysis¹⁹ differs from the earlier analysis¹³ in excluding people with prior cardiovascular disease and including only those with a complete diabetes risk factor profile. Thus the study population in the later analysis is about half as big as in the first analysis.



Author	Year(s)	Site(s)	n, F-U	Age*, M/F (%)	Diabetes risks	Incidence ⁺
Justman ¹⁷	1995-1998	US, WIHS	1435, 2.9 y	M 37, 0/100	55% black, 26% Hispanic, BMI 25.5	2.8% (20 of 707) on PI, 2.8/100 p-y; 1.2% (18 of 1486) on NRTIs only, 1.2/100 p-y; 1.2% (18 of 1480) not on ART, 1.2/100 p-y
Tien ¹⁸	2000-2006	US, WIHS	1524, 5.5 y	M 39.2, 0/100	56% black, 28% Hispanic, 30% family history, BMI 26.8, 47% current smoker, 30% HCV, 84% on ART	7.6% (116 of 1524); 2.5/100 p-y on PI; 2.89/100 p-y on non-PI ART; 3.4/100 p-y NRTIs only; 1.53/100 p-y no ART
Brown ¹⁰	1999-2003	US, MACS	319, 2.3 y	M 46, 100/0	Risk factors not reported for incidence population; see Table 1 for risk factors in prevalence population	4.7/100 p-y on ART; 1.7/100 p-y not on ART
De Wit ¹³	1999-2005	Europe, US, Australia, Argentina, DAD Study	32,437, 6 y	M 38, 74/26	13% nonwhite, BMI 23.0, 73% on ART, 58% on PI	2.3% (744 of 32,437), 0.57/100 p-y
Petoumenos ¹⁹	2000-2010	Europe, US, Australia, Argentina, DAD Study	16,632, 5.2 y	M 46.2, 73/27	7% nonwhite, 95% on ART, BMI 23.0, 25% HCV	2.7% (376 of 16,632), 0.42/100 p-y

Table 2. Diabetes incidence in Western HIV populations



Author	Year(s)	Site(s)	n, F-U	Age*, M/F (%)	Diabetes risks	Incidence ⁺
Rasmussen ²⁰	1996-2010	Denmark, HIV+/HIV- matched cohort comparison	3540, 8 y	M 38.7, 84/26	2.5% nonwhite, 86% on ART, 18% overweight or obese, 19% HCV	3.0% (105 of 3540), 0.37/100 p-y
Ledergerber ²¹	2000-2006	Switzerland, Swiss HIV Cohort Study	6513, 6 y	M 38, 69/31	15.5% nonwhite, BMI 22.5, HCV 27%, 73% on ART	1.9% (123 of 6513), 0.44/100 p-y
Polsky ¹¹	2002-2006	Bronx, New York	222, 1.55 y	M 50, 47/53	61% black, 27% Hispanic, 37% overweight, 24% obese, 79% on ART, 58% HCV	5.4% (12 of 222)
Capeau ²²	1997-2009	France	1046, 9.6 y	M 37, 79/21	10% black, BMI 22.1, 100% on ART (indinavir in 54%, d4T in 75%, ddI in 52%), 22% HCV	10.6% (111 of 1046), 1.41/100 p-y
Herrin ²³	1999-2013	US, Veterans Aging Cohort	2891, 5.5 y	48, 95/5	55% black, 28.5% overweight, 9.5% obese, 35.5% current smokers	9.2% (267 of 2891), 1.7/100 p-y
Tripathi ²⁴	1994-2011	US, South Carolina	6816, 5.8 y	M 39, 57/43	71% black, 21% white, 8% other, 80% on ART, 37% HTN, 10% documented obese, 8% HCV, 30% documented tobacco use	7% (491 of 6816) with HIV, 9% (595 of 6816) without HIV, 1.135/100 p-y with HIV, 1.360/100 p-y without HIV

*M, median; no M, mean.

†Diabetes mellitus defined (by reference number): **10**, fasting glucose \geq 126 mg/dL, self-reported diabetes diagnosis, self-reported use of antidiabetic medication; **11**, fasting glucose \geq 126 mg/dL, 120-min glucose \geq 200 mg/dL during OGTT, or antidiabetic medication; **13**, confirmed fasting blood glucose \geq 126 mg/dL, physician report plus antidiabetic medication; **17**, self-report or diagnosis or antidiabetic medication since last visit; **18**, fasting glucose \geq 126 mg/dL, reporting antidiabetic medication, or reporting diabetes diagnosis (with subsequent confirmation by fasting glucose or antidiabetic medication; **20**, Danish National Hospital Registry code for diabetes mellitus or antidiabetic medication; **22**, confirmed glucose \geq 126 mg/dL, 120-min glucose \geq 200 mg/dL, during OGTT, or antidiabetic medication (excluding metformin); **23**, hemoglobin A1c >6.5; **24**, at least two diabetes visit claims at least 30 days apart and/or antidiabetic medication.

ART, antiretroviral therapy; BMI, body mass index (kg/m²); F-U, follow-up; HCV, hepatitis C virus infection; HTN, hypertension; MACS, Multicenter AIDS Cohort Study; M/F, proportions male/female; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; p-y, person-years of follow-up; WIHS, Women's Interagency HIV Study.



Recent diabetes incidence lower with HIV

Seven of the 11 diabetes incidence studies—6 in the United States^{10,11,17,18,23,24} and 1 in Denmark²⁰ compared incidence between the HIV group and an HIV-negative comparison set (**Table 3**). Four studies found a significant difference in incident diabetes risk between the HIV group and the non-HIV group,^{10,20,23,24} and in three of those studies having HIV predicted a lower risk of new diabetes.^{20,23,24} In Denmark the largest of these comparisons found a higher diabetes risk with HIV only in the early combination antiretroviral years (1996-1998),²⁰ when HIV-positive people still took antiretrovirals that warped glucose metabolism. In more recent years (1999-2010), diabetes risk was similar in people with and without HIV (**Table 3**). When the researchers limited the 1999-2010 analysis to the time before people started antiretroviral therapy, the HIV group had a 55% lower diabetes risk (adjusted IRR 0.45, 95% CI: 0.21 to 0.96).

In contrast to these results, the MACS study found a 4-fold higher diabetes rate in HIV-positive men taking antiretroviral therapy than in HIV-negative men (**Table 3**).¹⁰ But this 1999-2003 study included many men taking outmoded unboosted PIs (including ritonavir and indinavir) and toxic nucleosides (stavudine, zidovudine, and didanosine) that may affect glucose metabolism. The MACS team later determined that every year taking nucleosides of this vintage boosted odds of high insulin 8%.²⁶

Table 3. Diabetes incidence in HIV cohorts versus control col	orts
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	W	ith HIV	With	out HIV
Author	n, risk factors	Incidence/100 p-y	n, risk factors	Incidence/100 p-y
Justman ¹⁷ 1995-1998, WIHS	1435, age 37, 55% black, 26% Hispanic, BMI 25.5*	2.8 on PI 1.2 on NRTIs only 1.2 not on ART	350, age 36, 52% black, 30% Hispanic, BMI 26.4*	1.4 (P = 0.06 vs HIV group on PI; no other differences) Trend to higher diabetes rate in HIV-positives on PI
Tien ¹⁸ 2000-2006, WIHS	1524, age 39.2,* 56% black, 28% Hispanic, BMI 26.8,* HCV 30%*	2.5 on PI 2.89 non-PI ART 3.4 NRTIs only 1.53 no ART	564, age 34.3,* 58% black, 27% Hispanic, BMI 28.0,* HCV 16%*	1.96 (not significantly different from any HIV group) No difference
Brown ¹⁰ 1999-2003, MACS	319†	4.7 on ART 1.7 not on ART	361†	1.4 (relative rate 4.11 for HIV group on ART vs non-HIV group) Higher diabetes rate in HIV-positives on ART

	w	/ith HIV Without HIV		
Author	n, risk factors	Incidence/100 p-y	n, risk factors	Incidence/100 p-y
Polsky ¹¹ 2002-2006, Bronx, New York	222, age 50, 61% black, 27% Hispanic, 61% overweight or obese, HCV 42%	5.4% (12 of 222)	155, age 50, 46% black, 34% Hispanic, 69% overweight or obese, HCV 43%	8.4% (8 of 155) Lower diabetes rate in HIV-positives
Rasmussen ²⁰ 1996-2010, Denmark	3540, age 38.7, 2.5% nonwhite, 18.1% overweight or obese	0.37	14,160, age 38.7	0.387 For HIV+ vs HIV-: IRR 1.02 overall IRR 2.83 in 1996-1998 IRR 0.90 1999-2010 IRR 0.45 1999-2010 before ART begins Similar or lower diabetes rates in HIV-positives vs negatives after early combination ART years
Herrin ²³ 1999-2013, Veterans Aging Cohort Study	2891, age 48, 55.4% black, 38% overweight or obese	1.7	7567, age 50, 47.7% black, 72.5% overweight or obese	3.1 (hazard ratio 0.74, <i>P</i> < 0.001, for HIV group vs non-HIV group) Lower diabetes rate in HIV-positives
Tripathi ²⁴ 1994-2011, South Carolina	6816‡	1.135	6816‡	1.360 (adjusted hazard ratio 0.55 for HIV group on ART vs non-HIV group) Lower diabetes rate in HIV-positives

Table 3. Diabetes incidence in HIV cohorts versus control cohorts (continued)

For details on participant demographics and follow-up, see Table 2. ART, antiretroviral therapy; BMI, body mass index (kg/m²); HCV, hepatitis C virus; IRR, incidence rate ratio; MACS, Multicenter AIDS Cohort Study; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; WIHS; Women's Interagency HIV Study.

*Asterisk indicates significant difference by HIV status.

†Risk factors not reported separately for HIV-positive and negative men in the incidence population. See Table 1 for risk factors in prevalence population.

‡Matched groups.



A Women's Interagency HIV Study (WIHS) analysis discerned a trend toward higher diabetes risk in women on PI therapy than in HIV-negative women (incidence 2.8 versus 1.4 per 100 p-y, P = 0.06).¹⁷ But this study dates to the dawn of the combination therapy era (1995 to 1998) when most people took unboosted indinavir, ritonavir, or saquinavir and first-generation nucleosides. In a small Bronx cohort a lower proportion of people with than without HIV had newly diagnosed diabetes (5.4% versus 8.4%), but the authors did not report significance calculations.¹¹ The three studies that calculated lower incident-diabetes risk in people with HIV, or equivalent risk in people with and without HIV, are also the largest and most recent studies that compare incidence by HIV status.^{20,23,24} If we put these pieces together, it appears that HIVpositive people may have run a greater risk of diabetes in the early days of combination antiretroviral therapy, but that today better care of people with HIV with safer antiretrovirals has reversed that risk balance. HIV metabolic experts like Jacqueline Capeau (University Pierre and Marie Curie, Paris) argue that certain HIV groups may sidestep some common chronic diseases more often than HIV-negatives because they see their clinician much more regularly than people without HIV, because they get screened for comorbidities more often, and because awareness of these mortal diseases runs high in the HIV community.

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Diabetes risk, screening, and monitoring in people with HIV

An interview with Todd T. Brown, MD, PhD

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Dr. Brown is Associate Professor of Medicine and Epidemiology at Johns Hopkins University in Baltimore and the primary endocrine consultant to the Johns Hopkins HIV Clinic. He holds an MD from the Columbia College of Physicians & Surgeons and a PhD from the Johns Hopkins Bloomberg School of Public Health. Over the past decade, Dr. Brown has become a leading authority on metabolic, endocrine, and skeletal abnormalities in people with HIV infection, particularly as those conditions relate to aging. A coinvestigator in the Multicenter AIDS Cohort Study (MACS), he chairs that cohort's Metabolic Working Group. In the AIDS Clinical Trial Group (ACTG), Dr. Brown is a member of the Inflammation/End Organ Disease Transformative Science Group and serves in leadership positions on multiple studies. Since 1995 he has coauthored over 70 reports of original research in peer-reviewed publications and has contributed eight book chapters.

Is HIV a diabetes risk factor?

Mascolini: Many HIV populations have high frequencies of classic diabetes risk factors, but is HIV itself a risk factor?

Brown: This is a controversial question: different cohorts have different results. Some cohorts like the MACS found a clear increase in the prevalence and incidence of diabetes in HIV-infected people compared with uninfected controls.¹ This has also been seen in the Women's Interagency HIV Study (WIHS)² and in several other cohorts. But other cohorts such as the Veterans Aging Cohort Study (VACS) have seen quite the opposite—that HIV-

infected patients in the VA system have a lower incidence of diabetes than veterans without HIV.³ So I think the impact of HIV on diabetes risk is probably population-dependent.

What we're seeing with HIV and diabetes is similar to what we see for other comorbidities: HIV disease itself may have some impact, antiretroviral therapy may have an impact, and traditional risk factors for the comorbidity are also critically important. We can look at each of those factors in turn.

For HIV disease itself, we know that HIV is associated with chronic inflammation. Even patients who have undetectable viral loads have residual inflammation that's thought to lead to comorbidities, and diabetes is one of them. We showed in the AIDS Clinical Trials Group that TNF receptor levels 48 weeks after antiretroviral initiation, when people had a suppressed viral load, were associated with incident diabetes.⁴ From that perspective, HIV is probably an independent risk factor for diabetes.

The next category is the effect of antiretrovirals. Antiretrovirals have changed quite a bit since the introduction of highly active antiretroviral therapy (HAART): In general the medications have become a lot more metabolically friendly, and this improvement definitely includes effects on glucose metabolism. In the late 1990s, soon after widespread uptake of HAART, research showed that early protease inhibitors (PIs) had a marked effect on glucose metabolism. PIs have gotten better over the course of the past 15-plus years, and currently used PIs have relatively modest effects on glycemia. Thymidine nucleoside analogs, particularly stavudine, were also associated with abnormal glucose metabolism, not only through direct effects, but also indirectly by inducing lipoatrophy, which in turn is associated with insulin resistance and diabetes onset.

Probably the biggest drivers of diabetes in HIV populations are traditional risk factors—mainly increased adiposity and obesity. We're seeing high rates of obesity in HIV populations, just as we are in the general population, and this is the biggest driver of the diabetes epidemic in the United States. The other major factor of course is age. The HIV population is getting older, and age is a major diabetes risk factor.

Other reasons why HIV patients may have an increased risk of diabetes are other infections: Hepatitis C infection is associated with abnormal glucose metabolism, and this may contribute to diabetes in HIV/HCV-coinfected patients. Concomitant medications may also play a role. Steroids have a huge effect on glucose metabolism, and for patients taking medications that interfere

with steroid metabolism—such as ritonavir and cobicistat—this may be a particular problem. Also, some HIV patients take atypical antipsychotics, which can increase diabetes risk by increasing weight and also through an independent effect on glucose metabolism.

The bottom line is that HIV patients can have several diabetes risk factors that HIV-uninfected patients don't have, so they may be at higher risk for diabetes.

Mascolini: What's going on in your own patient population in terms of diabetes incidence? Have you seen any change over the past decade or since the introduction of combination antiretroviral therapy?

Brown: It's a little tricky to tease this apart because we saw overall exponentially increased rates of diabetes in the general population during this time. I think diabetes incidence may have decreased slightly in HIV patients during the HAART era as the medications got better, and a cohort study in France showed this quite nicely.⁷ But because as a population we're getting fatter, overall diabetes rates are very high, not only in HIV populations but in the general population. Perhaps the specific impact of antiretroviral therapy on diabetes incidence has decreased over this time, but the overall rates of diabetes have actually increased, probably because of increased adiposity.

Impact of newer antiretrovirals

Mascolini: Older antiretrovirals like d4T and indinavir were linked to glucose abnormalities. Among antiretrovirals often prescribed today, do any pose a risk of dysregulated glucose?

Brown: Glucose metabolism and adiposity generally get worse after antiretroviral initiation. This effect is probably driven by the fat increase many people have

continued...

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Tips from this interview on diabetes management in people with HIV

- The impact of HIV itself on diabetes risk remains controversial, but there is no question that HIV populations carry a heavy burden of traditional diabetes risk factors.
- The hemoglobin A1c test underestimates blood glucose in people with HIV. A hemoglobin A1c of 6.5% in an HIV patient may be equivalent to 7.0% in an HIV-uninfected patient, so this test should probably not be used to screen for diabetes in people with HIV.
- Hemoglobin A1c targets for diabetes treatment should probably be individualized, with more stringent targets (6.0% to 6.5%) for younger people without comorbidities, and looser targets (7.0% to 8.0%) for older people with comorbidities and thus a higher risk of hypoglycemia.
- High mean corpuscular volume (MCV) is a strong predictor of hemoglobin A1c/glycemia discordance. If I see an MCV in the high 90s or over 100 in an HIV-infected patient, I know not to trust the HbA1c too much.
- The dose of saxagliptin, an oral hypoglycemic agent, may need to be lowered to 2.5 mg when given with a potent CYP3A4 inhibitor.⁵
- The HIV integrase inhibitor dolutegravir increases metformin plasma exposure and may necessitate downward dose adjustment of metformin.⁶
- Whether an HIV patient with diabetes should be referred to an endocrinologist depends on the provider's comfort level in managing diabetes. Bear in mind that specialists have an array of resources that can improve diabetes management, like certified diabetes educators and nutritionists.

after starting antiretroviral therapy. One outstanding question is whether this is a return-to-health phenomenon that is part and parcel of getting better from HIV, or whether it is a maladaptive response and whether the proportion of fat versus lean mass is abnormal in people who start antiretroviral therapy. But I don't think there are big differences between individual current antiretrovirals in terms of their effects on glucose metabolism.





ACTG A5257 was a study of HIV-infected treatmentnaive patients initiating either ritonavir-boosted atazanavir, boosted darunavir, or raltegravir with tenofovir/emtricitabine.⁸ In the A5260 substudy of A5257, we looked at the effects of these three regimens on glucose metabolism and adiposity,⁹ and these results will be detailed at CROI in an oral presentation.

Mascolini: When you talk with primary HIV providers, do they seem to have a good understanding of how current antiretrovirals affect glucose or insulin?

Brown: Ithink there's an overemphasis on the effects of specific antiretrovirals on glucose metabolism. As we already discussed, some first-generation antiretrovirals had an important effect on glucose metabolism, but the agents used today generally don't. That's not to say there aren't some patients whose blood sugars become quite deranged while they're taking certain current antiretrovirals, probably for genetic reasons. But I think there's an overemphasis in the HIV community on how much currently prescribed antiretrovirals affect glucose metabolism.

Advice on screening HIV patients for diabetes

Mascolini: In your group at Hopkins, what's the protocol for glucose screening and follow-up for a person with newly diagnosed HIV?

Brown: The HIV guidelines in place right now suggest that we should get some measure of glucose metabolism and screen for diabetes at the time of HIV diagnosis, after 3 to 6 months of antiretroviral therapy, and yearly thereafter. These guidelines were written earlier in the HAART era, when we were seeing a large effect of antiretroviral therapy on glucose metabolism. Today this recommendation might be a little bit of overkill. However, the tests to

screen for diabetes are relatively benign and relatively low in cost, so it probably does make sense to get these fasting tests when you're getting fasting lipids, for example.

The American Diabetes Association recommends diagnosing diabetes with one of four tests: (1) a fasting glucose, with 126 mg/dL or higher indicating diabetes, (2) a 2-hour 75-g oral glucose tolerance test, with 200 mg/dL or greater considered diabetes, (3) a random glucose with symptoms of diabetes polyuria and polydipsia—and a diagnostic cutoff of 200 mg/dL or higher, or (4) hemoglobin A1c (HbA1c), which came online in 2010.

Hemoglobin A1c has some advantages over the other tests in that it needs no special preparation—patients don't have to fast before the test or swallow a glucose solution. Also, instead of giving you a one-pointin-time look at glucose, which can bounce around a little bit, it gives you an integrated view over 3 months, which is the life of the red blood cell: The test calculates glucose by measuring its attachment to a hemoglobin moiety in red blood cells. Because of these advantages, hemoglobin A1c is quite attractive.

The caveat is that the hemoglobin A1c may underestimate glycemia in HIV patients.¹⁰ The effect of this underestimation is somewhere between 0.2 to 0.5 hemoglobin A1c percentage points. A hemoglobin A1c of 6.5% in an HIV patient may be equivalent to an HbA1c of about 7.0% in an HIVuninfected patient. This makes the use of hemoglobin A1c for the diagnosis of diabetes a little bit tricky in HIV-positive patients. It could potentially lead to the underdiagnosis of diabetes in people with HIV. For that reason I generally recommend that we stick to the fasting glucose tests for screening.

The reasons behind this hemoglobin A1c discordance in people with HIV aren't entirely clear. HIV



patients may have a low-grade hemolysis that causes increased red blood cell turnover and an artificial lowering of hemoglobin A1c—that is, a disconnect between glycosylation of the hemoglobin molecule and what the actual blood glucose is.

One very strong risk factor for hemoglobin A1c/ glycemia discordance that has been seen in multiple studies, including our work in the MACS,¹⁰ is a high mean corpuscular volume (MCV). The higher the MCV is over 90 or so, the greater the hemoglobin A1c/glycemia discordance. This is useful clinically since MCV is routinely measured on a complete blood count (CBC). In my practice, if I see an MCV in the high 90s or over 100 in an HIV-infected patient, I know not to trust the HbA1c too much. The reasons underlying this association are unclear, but we hypothesize that these larger red cells are taken out of circulation more quickly than normalsize cells.

Mascolini: Does hemoglobin A1c have a role in monitoring patients once they start treatment for high blood glucose?

Brown: I do follow the A1c in HIV patients because it is a critical measure. One of the important developments in the diabetes world over the past few years is the individualization of the hemoglobin A1c goal. We used to shoot for a hemoglobin A1c less than 7.0% in everyone.

Now the recommendation is to take a more individualized approach. For people at potentially higher risk for hypoglycemia or with comorbidities, the recommendation is to relax the hemoglobin A1c target to between 7 and 7.5, and in some cases up to 8. For younger people who don't have comorbidities, you might push them a little bit harder to reach a lower A1c target. For an HIV patient, I take that individualized approach and might push them a little bit harder, knowing that their hemoglobin A1c may be an underestimate of their real glycemia.

Referral and antiretroviral interactions

Mascolini: Are there glucose-related clinical developments in HIV patients that should prompt HIV clinicians to refer those patients to an endocrinologist?

Brown: Referral really depends on how comfortable the provider is in dealing with diabetes. As an endocrinologist, I see patients with the full gamut of severity of diabetes. Some physicians get me involved after a patient has tried one drug, for example, metformin, and they clearly need additional drugs. Other providers will get me involved when two drugs have failed. Others will call me in when a patient has diabetes complications that make overall care complicated. Others will get me involved when the consideration of insulin is on the table.

So it depends on the provider's comfort level and infrastructure in dealing with diabetes. It is a resourceintensive disease, and oftentimes endocrinologists might be better equipped in terms of having certified diabetes educators and nutritionists available to help care for these patients.

Mascolini: Are there any other clinical issues related to HIV and diabetes that you'd like to bring to the attention of HIV clinicians?

Brown: One important issue with all comorbidities is the potential interaction between antiretrovirals and drugs used to treat the comorbidities. In the diabetes world we've been fortunate in that many of





Making diet and exercise part of the glucose-control plan INVITEDARTICLE **FUVALOS** Konsth H. Mayer, Sector Editor Diagnosing and Managing Diabetes in HIV-Infected Patients: Current Concepts Anne K. Monroe,¹ Marshall J. Glesby,² and Todd T. Brown³

- "Referral to a registered dietician for medical nutrition therapy is recommended for all patients with diabetes mellitus, as even modest weight loss (as little as 2 kg) can have an impact on glycemic control.
- "Calorie guidelines for weight loss are (1) 1200–1500 calories/day for women or 1500–1800 calories/day for men; (2) an energy deficit of 500 or 750 calories per day, based on the individual; or (3) an evidence-based diet that restricts a certain food type (eg, high-carbohydrate foods) to create an energy deficit.
- "Dietary recommendations for patients with DM include monitoring carbohydrate intake, limiting consumption of sugar-sweetened beverages, and following a Mediterranean-style diet.
- "A patient-friendly diet guide is available at (http://www.diabetes.org/food-and-fitness/food/what-can-i-eat/).
- "Aerobic exercise is recommended for at least 150 minutes a week, spread out over at least 3 days per week, along with strength training twice a week.
- "An exercise partner, use of a pedometer with a target (eg, 10 000 steps/day), or individualized counseling with exercise prescription" may encourage people to exercise.
- "Linking patients with community- or workplace-based programs may increase exercise uptake."

The article also analyzes the impact of antiretrovirals and statins on diabetes risk, individualized management of diabetes, drug therapy for diabetes, comprehensive cardiovascular risk reduction, and other issues.

Monroe AK, Glesby MJ, Brown TT. Diagnosing and managing diabetes in HIV-infected patients: current concepts. *Clin Infect Dis.* 2015;60:453-462.



the drugs used to treat diabetes can be used without a problem in HIV-infected patients regardless of what antiretrovirals they're taking.

There are a few notable exceptions. Some of the new DPP-4 inhibitors—the gliptin class of hypoglycemics can interact with antiretrovirals. Saxagliptin, for example, is a substrate for CYP3A4, so it should probably be avoided in HIV-infected patients taking a CYP3A4 inhibitor like ritonavir or cobicistat.⁵ The other interaction that can affect many HIV patients with diabetes is the interaction between metformin and the integrase inhibitor dolutegravir.⁶ Depending on the dose of dolutegravir, metformin concentrations can increase by 50% to 100%. So I generally go with metformin dose reductions in those patients. That's an important interaction that clinicians should know as more and more patients start integrase inhibitor-based regimens.

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Perspectives

Standards of care and standards of screening for high glucose with HIV

By Mark Mascolini

Abstract: US clinicians appear to guide HIV patients to appropriate glucose targets as often as they do patients without HIV, but only about one half of patients meet the strictest glucose goal. Glucose targets may need to be tighter for some-but not all-HIV-positive people than for the general population. Reaching glucose targets cuts the risk of vascular complications. Treating HIV-positive people with high glucose should include active management of lipids and hypertension plus regular retinal and foot exams. Clinicians have four tools to screen for diabetes and monitor treatment response in people with high glucose: fasting blood glucose, hemoglobin A1c (HbA1c), the oral glucose tolerance test (OGTT), and random glucose. Several studies show that HbA1c underestimates blood glucose in people with HIV and some experts recommend avoiding it to screen for diabetes in HIV populations. US guidelines say the role of OGTT in HIV-positive people is "uncertain," but it may be appropriate for people with multiple risk factors.

How often do US clinicians meet American Diabetes Association (ADA) treatment goals in HIV-positive people with diabetes? At two big urban HIV centers in Chicago¹ and New York,² HIV providers hit glycemic goals in one half to three quarters of patients—depending on the hemoglobin A1c (HbA1c) target—close to rates reported in the general population (**Table 1**).

But only about half of diabetic HIV patients in these cohorts met ADA blood pressure goals, and only one third nailed triglyceride targets. Clinicians at both sites admitted they may have overestimated proportions of on-target patients because they eliminated people with fewer visits or hemoglobin A1c measurements. And neither survey looked at how rigorously clinicians screen HIV patients for high glucose, insulin resistance, or diabetes—or how well they manage prediabetes.

Keen attention to glucose abnormalities and their control in people with HIV assumes growing importance as these complications loom larger in HIV populations. From the mid-1990s to the mid-2000s, US hospital admissions for diabetes rose 2.2-fold in people with HIV compared with 1.4-fold in HIV-negative people.³ Although studies disagree on whether HIV infection independently boosts chances of diabetes, this chronic disease clearly adds to myocardial infarction risk in people with HIV^{4,5} and can cause or contribute to kidney disease, liver disease, stroke, cognitive decline, and other HIV-linked maladies.

Meeting metabolic treatment targets (or not)

The retrospective diabetes-control studies took place at Chicago's CORE Center¹ and New York's Weill Cornell Medical College,² where HIV clinics care for thousands of patients yearly in a uniform, multidisciplinary manner and staffs have logged countless hours of experience caring for people with HIV. High proportions of HIV/ diabetes patients at both centers were black or Hispanic, average age topped 50 years, and mean body mass index verged on the obesity threshold (**Table 1**). All study participants were adults with diabetes established by standard measures. Almost all took antiretrovirals and most had an undetectable viral load (**Table 1**).

Both research teams calculated proportions of HIV diabetes patients who met two 2008 ADA goals for HbA1c—below 7% or below 8%. (Current ADA



	Chicago (n = 216) ¹	New York City (n = 142) ²
Blacks/Hispanics/whites (%)	67/23/10	39/37/18
Men/women (%)	72/28	66/34
Average age	51	52
Average body mass index (kg/m²)	28.3	28.7
Current smokers (%)	30*	25
Taking ART/undetectable VL (%)	98/72	92/56
	Metabolic targets	
HbA1c <7%/<8% (%)	54/72	57/78
Blood pressure <130/80 mm Hg (%)	56	42
Total cholesterol <200 mg/dL (%)	71	NR
LDL cholesterol <100 mg/dL (%)	56	66
HDL cholesterol >40/50† mg/dL (%)	51	32
Triglycerides <150 mg/dL (%)	39	31

Table 1. Glycemic and other metabolic targets achieved in two US HIV clinics

ART, antiretroviral therapy; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NR, not reported.

* Smoking status not documented in 28%.

 $\ensuremath{^+}$ HDL target >40 mg/dL in men, >50 mg/dL in women.

guidelines suggest HbA1c goals ranging from below 6.5% to below 8%, depending on patient traits and risk of diabetes treatment side effects.⁶ Normal HbA1c lies below 5.7%.⁷)

For the general population, HbA1c is the main test used to manage and study diabetes.⁷ It measures attachment

of glucose to hemoglobin in red blood cells. Because red cells live about 3 months, HbA1c determines a person's average blood glucose over the past few weeks to 3 months—an advantage over the glucose snapshot with fasting glucose assays. Whether a person has fasted for 24 hours or just gobbled six glazed donuts has no impact on HbA1c-measured glucose, whereas a straight

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measure of glucose in blood requires fasting. Studies reviewed below indicate that HbA1c underestimates blood glucose in people with HIV. (See **"Screening for high glucose"** below for HbA1c use in people with HIV.) US experts are divided on using HbA1c as a way to test HIV patients for diabetes.⁸⁻¹⁰

Proportions of HIV-positive diabetes patients who reached HbA1c targets proved similar in the two studies—54% in Chicago¹ and 57% in New York² below 7%; 72% in Chicago and 78% in New York under 8% (**Table 1**). Chicago did better in getting diabetes patients to hit a blood pressure goal below 130/80 mm Hg—56% versus 42% in New York. Chicago also had a much higher proportion of patients on target for HDL cholesterol (51% versus 32%), while both clinics struggled to guide patients toward a triglyceride tally below 150 mg/dL (39% and 31%). The New York group noted that only 47% of their patients had eye exams for retinopathy, and only 19% got screened for microalbuminuria.

Both research teams observed that HbA1c goal attainment in their HIV patients with diabetes mirrors or exceeds findings in the general population.^{1,2} Both teams also suggested their results may exceed those in broader US HIV populations because they included only people with two or more clinic visits in 1 year (and thus possibly represented a more engaged population) and because both centers provide multidisciplinary teams with deep HIV experience.

Regardless of such variables, reaching a treatment goal in about half of patients might well be deemed failure. It is, for example, when the endpoint is proportion of patients with an undetectable HIV load. The Chicago and New York clinicians offer colleagues several suggestions for improving diabetes care in people with HIV (**Table 2**).

Managing prediabetes and diabetes in people with HIV

ADA experts outline treatment of high glucose in the general population,⁶ and those regularly updated guidelines form the basis for HIV-specific advice from the Health Resources and Services Administration (HRSA).⁸ As with treatment of other comorbidities in people with HIV, treatment of diabetes can be complicated by the retrovirus, by certain antiretrovirals, and by conditions frequently seen in HIV populations.

The goal of diabetes therapy in HIV-positive people, HRSA advises,⁸ is to keep HbA1c below 7% while avoiding hypoglycemia. Hypoglycemia is more common with insulin therapy than with most oral antidiabetics, HRSA says.

In a recent review of diabetes and HIV, Anne Monroe and Todd Brown from Johns Hopkins University and Marshall Glesby from Weill Cornell Medical College offered some pointers on setting treatment targets with HbA1c, suggesting that the goal "may need to be more stringent" in people with HIV than in the general population because HbA1c underestimate glucose levels in HIV populations (see next section).¹⁰ Reaching glycemic targets may reduce vascular complications of diabetes, research indicates, but "more intensive

Table 2. Strategies for improving diabetes care in people with HIV^{1,2}

- Checklists of recommended screening procedures for providers and patients
- Ongoing education of HIV providers on up-to-date care of metabolic diseases
- Multidisciplinary approach to diet, adherence, glucose monitoring, and exercise advice
- Patient group sessions on home glucose monitoring, nutrition, and foot care



glucose control" has its downside—a higher risk of severe hypoglycemia and death. The Hopkins-Cornell team suggested "tighter control (HbA1c 6.0% to 6.5%) is more appropriate for younger, healthier patients, whereas looser control (HbA1c 7.5% to 8.0%) may be more appropriate for older patients with multiple comorbidities who are prone to hypoglycemia."¹⁰

HRSA guidelines say metformin remains the drug of choice for high glucose in overweight people, but prescribers should avoid it in people with lipoatrophy, which metformin can worsen.⁸ Some sulfonylureas should be avoided in people with creatinine clearance below 50 mL/min, and thiazolidinediones (the glitazones) should not be given to people with "significant liver disease." Studies disagree on whether rosiglitazone boosts myocardial infarction risk. But both rosiglitazone and pioglitazone have been linked to congestive heart failure (CHF) and should not be used in people with CHF.⁸

HRSA guidelines add this advice for managing HIVpositive people with high glucose:

- Treat abnormal lipids and hypertension.
- Cut cardiovascular risk through lifestyle modification (exercise, weight loss, smoking cessation, moderate alcohol intake).
- Measure urine microalbumin and creatinine.
- Schedule a yearly retinal exam.
- Perform an annual foot exam.
- Start 75 to 162 mg of aspirin daily in people with macrovascular disease or a history of vascular events.
- Consider daily aspirin for people with higher coronary heart disease risk.

Can aggressive management of diabetes and its comorbidities prolong life? Yes, indeed, according to

a 13-year randomized trial of 160 people in Denmark with type 2 diabetes and persistent microalbuminuria.¹¹ Steno-2 Study investigators randomized them to standard care or to "intensified, target-driven therapy" including behavior modification, antiplatelet therapy, blood pressure management, cholesterol management, and diabetes/glucose management. After an average 7.8 years of treatment and 5.5 years of further observation, people in the intensive-care arm had almost a 50% lower risk of death, a 60% lower risk of cardiovascular death, and a 60% lower risk of cardiovascular events. The intensive regimen had few major side effects.

Monroe, Glesby, and Brown offer a concise review of diabetes treatment, covering initial management, switching antiretroviral regimens, diet, exercise, metformin, second-line treatments, sulfonylureas, thiazolidinediones (glitazones), insulin, incretins, and other agents.¹⁰

Screening for high glucose: where does HbA1c fit in?

Given the high morbidity and mortality of diabetes mellitus—and difficulties reaching glucose targets in people with HIV (**Table 1**)—spotting poorly controlled blood sugar early has become a keystone of HIV care. HIV Medicine Association (HIVMA) experts recommend screening everyone with HIV every 6 to 12 months by measuring fasting blood glucose and/ or HbA1c.⁹ They advise screening before antiretroviral therapy begins and 1 to 3 months after starting or changing regimens. Fasting blood glucose between 100 and 125 mg/dL indicates prediabetes, and anything higher signals diabetes (**Figure 1**). An HbA1c below 5.7% is normal, 5.7% to 6.5% means prediabetes, and anything higher indicates diabetes.

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Figure 1. Diabetes and prediabetes can be diagnosed in people with HIV with three principal assays. HIVMA recommends fasting blood glucose (FBG) and/or hemoglobin A1c.⁹ Evidence reviewed in the text indicates that HbA1c underestimates blood glucose in people with HIV, so some authorities question HbA1c use for diagnosing diabetes in HIV-positive people.¹⁰ The role of the oral glucose tolerance test (OGTT) in people with HIV is "uncertain,"⁸ but in the general population it is the preferred test for pregnant women. (Based on an American Diabetes Association illustration.¹²)

An oral glucose tolerance test (OGTT) may also be used to screen for glucose abnormalities (normal less than 140 mg/dL, prediabetes 140 to 199 mg/dL, diabetes 200 mg/dL or higher).⁸ A random glucose at or above 200 mg/dL in people with symptoms of hyperglycemia (thirst and frequent urination) also indicates diabetes.⁸ HRSA guidelines note that the role of the OGTT in HIV-positive people is "uncertain," but it may be appropriate for people with multiple risk factors.⁸ In the general population OGTT is, however, the preferred test for pregnant women, the ADA says.⁶ Patients must eat normally in the 3 days before an OGTT and fast 8 hours before the test, which takes up to 3 hours. ADA guidelines counsel that any test indicating diabetes should be repeated to rule out laboratory error, "unless the diagnosis is clear on clinical grounds," such as classic symptoms of hyperglycemia or hyperglycemic crisis.¹³ When two of these three tests (fasting glucose, HbA1c, or OGTT) disagree, repeat the test with a result above the diagnostic cut point and make the diagnosis based on the confirmatory test.

For HIV-positive people diagnosed with diabetes, HRSA recommends HbA1c monitoring every 3 months in people with an elevated value and every 3 to 6 months in those "with stable and adequate glucose control"⁸



Table 3. Monitoring HIV-positive people with diabetes

- HbA1c, every 3 months for patients with elevated HbA1c or whose antiretroviral therapy has changed, every 3 to 6 months for patients with stable and adequate glucose control
- Fasting lipid panel
- Electrolytes, creatinine, estimated glomerular filtration rate (eGFR)
- Urine albumin/creatinine ratio (microalbuminuria: 30 to 299 mg/g)

Source: HRSA Guide for HIV/AIDS Clinical Care.8

(**Table 3**). The goal should be a value below 7%. But using and interpreting HbA1c to screen for diabetes in HIV patients is more problematic, and guideline advice is inconsistent. HIVMA says HbA1c (or fasting glucose) "may be used to screen for glucose intolerance and diabetes" in people with HIV,⁹ while HRSA cautions that the test remains unvalidated for screening in HIVpositive people⁸ and Monroe, Glesby, and Brown advise against using HbA1c to screen for diabetes.¹⁰

Comparison of HbA1c and fasting glucose in HIVpositive and HIV-negative at-risk men in the Multicenter AIDS Cohort Study (MACS) found that HbA1c underestimates blood glucose in men with HIV.¹⁴ The analysis involved 1357 HIV-positive men and 1500 HIV-negative men seen at a median of 11 visits over 13 years. The MACS team used the relationship between HbA1c and fasting glucose in HIV-negative men to determine expected HbA1c in HIV-positive men.

When blood glucose stood at 125 mg/dL, HbA1c values lay a median 0.21% lower in men with versus without HIV.¹⁴This difference widened at higher glucose levels. Nearly two thirds of the HIV group (63%) had at least one visit with clinically significant HbA1c discordance (defined as an observed/expected HbA1c at or below -0.5%). The investigators found that discordance was independently associated with four variables:

- 1. CD4 count below 500 cells/mm³
- 2. Use of a protease inhibitor, a nonnucleoside, or zidovudine
- 3. High mean corpuscular volume
- 4. Abnormal corpuscular hemoglobin

Other research indicates that use of abacavir boosts chances of HbA1c inaccuracy.¹⁵

Summarizing this largest comparison of HbA1c in people with and without HIV, the MACS researchers concluded that "HbA1c underestimates glycaemia in HIV-infected patients and its use in patients with risk factors for HbA1c discordance may lead to underdiagnosis and to under-treatment of established diabetes mellitus."¹⁴

Four previous studies in more than 500 men and women with HIV also found that HbA1c underestimates blood glucose.¹⁵⁻¹⁸ Women's Interagency HIV Study (WIHS) investigators have observed that, besides high mean corpuscular volume and anemia, factors that can contribute to HbA1c inaccuracy are chronic alcoholism and acute blood loss.¹⁹ On the other hand, they noted, African Americans have higher HbA1c values than whites with similar glucose concentrations.²⁰ At the same time, the WIHS team found that using fasting blood glucose plus HbA1c to screen for diabetes enhances



diagnostic accuracy compared with fasting blood glucose alone in an analysis of 150 HIV-positive women and 550 HIV-negative women.¹⁹

Clinical investigators at a large New York City hospital calculated the sensitivity and specificity of HbA1c in identifying new diabetes in 395 antiretroviral-treated people with HIV.²¹ (Sensitivity is the ability of a test to identify people who have a disease; specificity is the ability of that test to classify people who do not have the disease as negative.) A fasting blood glucose at or above 126 mg/dL determined that 22 people had newly diagnosed diabetes. At a cutoff of 6.5%, HbA1c had a sensitivity of only 40.9% but a specificity of 97.5% in identifying fasting glucose-determined incident diabetes. When the researchers set the HbA1c cutoff at 5.8% (indicating prediabetes), sensitivity improved to 88.8% while specificity dropped to 77.5%. This finding encouraged the HIVMA to suggest using a 5.8% threshold for people with HIV.9

Studying 352 adults with or at risk for HIV infection in the Bronx, New York, researchers found that fasting blood glucose alone identified 52% of people with new hyperglycemia (prediabetes or diabetes determined by two fasting measures a median of 18.6 months apart).²² OGTT alone identified 33% of cases of new hyperglycemia, while fasting blood glucose plus OGTT identified 15%. In other words, relying solely on fasting blood glucose to screen for hyperglycemia misses one third of new cases in a group with or at risk of HIV. The HIV-positive and negative groups in this study both had a median age of 50.

What should HIV clinicians make of these knotty glucose monitoring findings? Colleen Hadigan and Sarah Kattakuzhy, HIV metabolic experts at the National Institutes of Health, suggest that, "for practical purposes, most investigators conclude that fasting blood glucose and HbA1c are the diagnostic tests of choice, and that there is not enough evidence in the HIV population to recommend for or against either strategy."²³

In contrast, HIV/diabetes mavens Anne Monroe, Marshall Glesby, and Todd Brown flatly say "we do not recommend using HbA1c for screening."¹⁰ They recommend fasting plasma glucose or the oral glucose tolerance test to diagnose diabetes in people with a shortened red-cell lifespan, such as pregnant women or people with hemolytic anemia. Monroe and colleagues add that discordant HbA1c results are more likely in people with a lower CD4 count, those taking nucleosides (especially abacavir), and those with higher mean corpuscular volume.

Because mean corpuscular volume predicted discordance between HbA1c and blood glucose, the MACS investigators believe clinicians should be "particularly cautious" in using HbA1c to diagnose or manage diabetes in people with a mean corpuscular volume at or above 95 fL.¹⁴ In such people, they found, odds of discordant HbA1c readings were 4- to 15-fold higher than in people with mean corpuscular volume below 95 fL. They also suggested that using complete blood counts to identify people with mean corpuscular hemoglobin above 31 pg "might serve as an alert that HbA1c levels need to be interpreted with caution."¹⁴

In the four HIV subgroups with high risk of HbA1c/ blood glucose discordance (numbered list above), the MACS team suggested using direct measures of glycemia—fasting blood glucose or OGTT—to diagnose diabetes and, for people with diabetes, "to consider a lower HbA1c level treatment target in order to prevent long-term diabetes complications."¹⁴



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Do plentiful diabetes risk factors include HIV?

By Mark Mascolini

Abstract: Whether HIV itself boosts diabetes risk remains controversial, but no one questions that HIV populations bear a weighty load of classic diabetes risk factors, including HCV infection, nonwhite race, older age, and treatment with drugs that affect glucose metabolism. Although currently favored antiretrovirals carry little or no risk of dysregulated glucose, many people with HIV take other drugs that may heighten diabetes risk, including corticosteroids, thiazides, statins, atypical antipsychotics, and niacin. Obesity remains the biggest driver of the US diabetes epidemic. Although a recent CDC study found lower obesity prevalence in people with HIV than in the general population, nearly one quarter of the HIV group was obese. The CDC calculated that 40% of HIV-positive US women are obese. Meta-analysis linked HCV infection to a two thirds higher diabetes prevalence or incidence, and one quarter of HIV-positive people in the United States have HCV infection.

Diabetes has many causes and many consequences (**Figure 1**). The immediate cause—upset glucose metabolism—is solitary. But factors that may contribute to runaway glucose readings are manifold. US Health Resources and Services Administration (HRSA) HIV guidelines list nine HIV risk factors,¹ including two HIV-specific factors, use of protease inhibitors (PIs) or nucleoside reverse transcriptase inhibitors (NRTIs), though currently favored antiretrovirals are kinder to glucose metabolism (**Figure 1**).

Whether HIV itself boosts diabetes risk remains hotly contested, but no one doubts that people with HIV bear a weighty risk burden. Besides taking antiretrovirals, HIV populations often have demographic and clinical features that pose a risk of unruly glucose, including nonwhite race, hepatitis C virus (HCV) coinfection, abnormal lipids, high blood pressure, and lipodystrophy. Older age ranks as an inescapable diabetes risk factor, and HIV populations across the world are aging. Although



Figure 1. Risk factors for type 2 diabetes (left) may be highly prevalent in HIV populations. Consequences of diabetes mellitus (right) often prove more frequent and severe in HIV groups than in the general population. (Pancreas from Servier PowerPoint image bank, *http://servier. com/Powerpoint-image-bank*.)



HIV-positive people in the United States tend to be leaner overall than people without HIV, obesity remains a problem in HIV-positive US women.

Myriad studies in people with and without HIV trace links between diabetes and dire clinical consequences:¹⁻⁶

- Cardiovascular disease (coronary artery disease, stroke, peripheral vascular disease)
- Kidney disease
- Liver disease
- Cognitive dysfunction and dementia
- Peripheral neuropathy
- Retinopathy

National Institutes of Health (NIH) metabolic experts Colleen Hadigan and Sarah Kattakuzhy counsel that "disorders of glucose metabolism" in people with HIV can culminate in "increased prevalence and worsened outcomes in a diverse array of conditions ranging from neurocognitive changes to renal impairment and albuminuria."²

Diabetes also has a telling impact on the ability of people with HIV to stay on the job, according to a study of 376 working-age HIV-positive people in France.⁷ Among these people diagnosed with HIV from 2004 through 2010, having diabetes boosted the risk of quitting work almost 6 times (adjusted hazard ratio [aHR] 5.7, 95% confidence interval [CI] 1.7 to 18.8, P = 0.005). The finding may sound self-evident, except that HIV disease severity had no impact on work.⁷ Neither did antiretroviral therapy or HIV-related discrimination. And diabetes proved a stronger job-ender than hypertension or depression.

Weighty impact of body mass index

Obesity and overweight stand at the top of any diabetes risk list, yet HIV populations generally weigh less than HIV-negative comparison groups. But HIV-positive women in the United States often do weigh too much. In a nationally representative 2009 sample of people with HIV, the Centers for Disease Control and Prevention (CDC) found that 23% are obese.⁸ In contrast, obesity prevalence stood at 36% in the US general population. Regardless of that difference, the finding that one quarter of US residents with HIV are obese is ominous.

The CDC calculated that 40% of HIV-positive US women are obese. Only 17% of HIV-positive men met standard obesity criteria in this analysis. Statistical analysis adjusted for age, race, poverty, years since HIV diagnosis, and durable viral suppression determined that HIV-positive women had a twice higher obesity rate than HIV-positive men (adjusted prevalence ratio 2.12, 95% CI 1.13 to 1.89). Almost everyone in this HIV sample, 95%, was taking antiretroviral therapy, 41% were non-Hispanic black, 35% non-Hispanic white, and 19% Hispanic.

Obesity emerges as a routine diabetes risk factor in HIV populations. In a 16,632-person DAD Study analysis, every additional mg/kg² of body mass index (BMI) independently raised the risk of newly diagnosed diabetes 10% (incidence rate ratio 1.10, 95% CI 1.08 to 1.13, P < 0.001).⁹ In an Italian comparison of 4249 people with HIV and 9148 healthy controls, diabetes prevalence rose from 3.2% in normal-weight HIV-positive people to 3.9% in overweight people with HIV and to 12.7% in the obese.¹⁰ Diabetes prevalence in the control group measured 1.1% in those of normal weight, 3.1% in the overweight, and 7.8% in the obese.

A person with HIV doesn't have to be obese, or even greatly overweight, to run a high risk of insulin resistance and diabetes because of weight abnormalities. Unhealthy visceral and subcutaneous fat build-ups affected insulin resistance in an analysis of 926 HIV-positive people representative of the US HIV population in the Fat Redistribution and Metabolic Change in HIV Infection

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(FRAM) study.¹¹ Body mass index in this HIV group (73% men, mean age 42.7) averaged only 25.1 kg/ m², on the lower end of overweight spectrum of 25 to 30 kg/m². Splitting HIV-positive people into three groups with the highest, medium, and lowest visceral and subcutaneous adipose tissue levels (VAT and SAT), FRAM investigators used multivariable analysis to determine that those in the highest VAT tertile had 3-fold higher odds of insulin resistance (HOMA above 4) than those in the lowest tertile (odds ratio [OR] 3.12, 95% CI 2.0 to 4.8, P < 0.0001). HIV-positive people in the highest trunk SAT tertile had twice higher odds of insulin resistance than those in the lowest tertile (OR 2.09, 95% CI 1.36 to 3.19, P = 0.001). A study of 345 antiretroviral-treated adults in Portugal confirmed a link between lipodystrophy and abnormal insulin and glucose.¹²

Some (but not all) studies buttress these intuitive associations between weight, fat, insulin resistance, and diabetes. A Women's Interagency HIV Study (WIHS) of 178 women with and at risk for HIV traced significant ties between higher BMI (P < 0.001) or more kilocalories from sweets (P = 0.025) and greater HOMA-measured insulin resistance.¹³ "Heavy-intensity physical activity" was associated with lower HOMA values (P = 0.006). The link between higher BMI and insulin resistance remained significant in an analysis limited to women with HIV (P < 0.001), while heavy-intensity activity proved marginally associated with lower HOMA (P = 0.06).

A cross-sectional Boston study of 207 antiretroviraltreated adults (more than 80% men) found an inverse association between Mediterranean Diet Score and HOMA-calculated insulin resistance—the higher (better) the score, the lower the insulin resistance (beta = -0.15, P = 0.03).¹⁴ The inverse association between Mediterranean Diet Score and insulin resistance held true in study participants with fat redistribution (beta = -0.13, P = 0.02).

But in an Australian study of 84 antiretroviral-treated men with lipodystrophy, dietary fat intake was not tied to total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, fasting insulin, glucose, or HOMA-measured insulin resistance.¹⁵ And fat subtypes could not be linked to fasting insulin, insulin resistance, glucose, total cholesterol, HDL cholesterol, or triglycerides.

But no one questions the central role of diet and exercise in maintaining a healthy body weight to avoid or control abnormal glucose. In the section on insulin resistance and diabetes, 2014 HRSA guidelines for HIV care stress the benefits of both a good diet (with advice from a dietician) and regular cardiovascular exercise.¹ HRSA lists "habitual physical inactivity" as a diabetes risk factor. For pointers on integrating diet and exercise into a diabetes care program, see the box on page 23.

Is HIV itself a diabetes risk factor?

Worthy statisticians who tried to disentwine HIV from other variables as a diabetes risk factor have reached two conclusions on whether HIV alone can lead to diabetes: Yes, it can. And no, it can't. One problem in any such analysis, no matter how large or refined, is residual confounding—the unassailable possibility that factors not melded into the covariate mix are swaying results one way or the other. And HIV populations typically shoulder a fugal array of diabetes risk factors. So it may be impossible to say whether HIV infection independently of other risk factors common to people with HIV—propels them toward a diabetes diagnosis.

Certainly one can imagine a rationale for why HIV, by itself, makes diabetes more likely. NIH metabolic mavens Colleen Hadigan and Sarah Kattakuzhy note that HIV-induced inflammation riles chemokines that regulate insulin and so could explain why HIV abets diabetes development.² As an example, they cite an AIDS Clinical Trials Group (ACTG) study that linked systemic inflammation after antiretroviral therapy (ART) began to new-onset diabtes.¹⁶ This case-control study compared 55 people diagnosed with diabetes



within 48 weeks of starting their first antiretroviral regimen and 55 controls matched for baseline BMI and race/ethnicity who remained free of diabetes. After adjustment for 48-week BMI and CD4 count, baseline marker levels, and indinavir use, people with higher initial levels of inflammation signals hsCRP, sTNFR1, and sTNFR2 had higher odds of a diabetes diagnosis. After further adjustment for week-48 glucose, higher sTNFR1 remained an independent predictor of diabetes (highest versus lowest quartile aOR 23.2, 95% CI 1.28 to 423, P = 0.03).

A more recent analysis of 3695 antiretroviral-treated people in the SMART and ESPRIT studies buttressed these findings, discerning links between higher inflammatory marker levels and newly diagnosed diabetes.¹⁷ During an average 4.6 years of follow-up, diabetes developed in 137 people. A regression model adjusted for baseline diabetes- and HIV-related factors determined that every doubling of IL-6 or hsCRP, two inflammation markers, nudged up the risk of incident diabetes (aHR 1.29, 95% CI 1.08 to 1.55, P = 0.005; aHR 1.22, 95% CI 1.10 to 1.36, P < 0.001).

But a study of 214 antiretroviral-naive people in France found no significant links between these same inflammation markers and insulin resistance in an analysis adjusted for age, sex, geographic origin, BMI, and waist circumference.¹⁸ This French analysis differs from the ACTG and SMART/ESPRIT studies in focusing on antiretroviral-naive people and in choosing a softer endpoint—insulin resistance rather than newonset diabetes. But one would prefer concordant results in all three studies to nail down the HIV \rightarrow inflammation \rightarrow diabetes hypothesis.

And if you look at studies weighing the impact of HIV as an independent diabetes risk factor, results are all over the map: Some find HIV does boost diabetes risk,^{10,19} others find it does not,²⁰⁻²² and others find a lower diabetes risk in antiretroviral-treated people with HIV than in comparison groups.^{19,21,23} Two studies reached two of these three conclusions, depending on the study period and antiretroviral use.^{19,21}

Two big cohort studies-one in Italy and one in Denmark-tagged HIV infection as an independent diabetes risk factor in comparisons with generalpopulation groups. A 2008 Italian study compared 4249 HIV-positive people attending a Milan infectious diseases clinic and 9148 healthy controls from 15 Italian regions (Table 1).¹⁰ About three quarters of both groups were men, median age was significantly younger in the HIV group (45.7 versus 46.6, P < 0.0001), and BMI was significantly lower (23.2 versus 25.3 kg/m², P < 0.0001). Median triglycerides were higher in the HIV group (126 versus 100 mg/dL, P < 0.0001). Diabetes prevalence proved significantly greater in the HIV group (4.1% versus 2.5%, P < 0.0001). After statistical adjustment for age, gender, BMI, triglycerides, and total, HDL, and low-density lipoprotein (LDL) cholesterol, chances of prevalent diabetes were 55% higher in people with HIV (aOR 1.55, 95% CI 1.02 to 2.31, P = 0.035).

The Milan investigators took a snapshot of diabetes prevalence in their study populations in 2008.¹⁰ A Danish study of similar size had the advantage of tracking diabetes incidence through more than a decade, from 1996 through 2010, in people with HIV and the general population.¹⁹ Denmark provides a unique platform for HIV research because everyone diagnosed with HIV in this country of 5.6 million people receives care at one of eight government HIV centers and gets tracked in a national database. The country also keeps detailed health records of the entire population that facilitate comparisons of HIV-positive and negative people.

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Author	n, year(s), age	M/F, race, BMI, ART	Risk factors* (95% CI)
Yoon, ²⁵ New York City (case-control study)	49, 1991-2000, A 45.1	63/37, 39% black, 35% Hispanic, 27% white, M 28.5, 82% NRTI use, 10% NNRTI use, 71% PI use	BMI: OR 1.13/kg/m ² (1.03-1.23) Family history: OR 5.55 (1.41-21.85) ALT: OR 1.16/10-unit higher (1.03-1.30) PI use, HCV not associated
Rasmussen, ¹⁹ Denmark (HIV+/ HIV- matched- cohort comparison)	3540, 1996-2010, M 38.7	84/26, 97.5% white, 18% overweight or obese, 86% on ART	HIV+ vs HIV- in 1996-1998: IRR 2.83 (1.57-5.09) HIV+ vs HIV- in 1999-2010 before ART begins: IRR 0.45 (0.21-0.96) Obese vs normal weight: IRR 9.25 (5.37-15.94) Age 60+ vs <30: IRR 8.16 (1.91-34.74) Lipoatrophy: IRR 2.30 (1.39-3.80) SQV use: IRR 1.53 (1.01-2.34) d4T use: IRR 1.81 (1.19-2.75)
De Wit, ²⁴ Europe, US, Australia, Argentina (DAD Study)	33,389, 1999- 2005, M 38	74/26, 13% nonwhite, M 23.0, 73% on ART, 58% on PI A 33,389-person DAD Study analysis linked nevirapine use to lower risk of new diabetes. ²⁴	d4T use: RR 1.13 (1.08-1.15) ZVD use: RR 1.05 (1.01-1.10) ddI use: RR 1.06 (1.01-1.11) RTV use: RR 0.90 (0.85-0.95) NVP use: RR 0.92 (0.86-0.99) HDL: RR 0.75/mmol/L higher (0.58-0.96) Trig: RR 1.64/doubling (1.50-1.80) Fat gain: RR 1.36 (1.09-1.68)
Tien, ²⁰ US (WIHS)	1524, 2000-2006, M 39.2	0/100, 56% black, 28% Hispanic, 16% white, M 26.8, 84% on ART	NRTIs >3 y: aRH 2.64 (1.11-6.32) 3TC >1 y: aRH 2.81 (1.33-5.95) HIV, PIs not associated
Galli, ¹⁰ Milan	4299, 2008, M 45.7	76/24, race not reported, 29.6% overweight or obese, 91.5% on ART	HIV: aOR 1.55 (1.02-2.31) [†] Age >50 vs \leq 50: aOR 3.77 (2.82-5.10) BMI 25-29.9 vs $<$ 25: aOR 1.59 (1.12-2.29) BMI \geq 30 vs $<$ 25: aOR 4.03 (2.72-5.99) HTN: aOR 1.34 (1.01-1.79)

Table 3. Independent risk factors for new-onset or prevalent diabetes in people with HIV



Author	n, year(s), age	M/F, race, BMI, ART	Risk factors* (95% CI)
Petoumenos, ⁹ Europe, US, Australia, Argentina (DAD Study)	16,632, 2000- 2010, M 46.2	73/27, 7% nonwhite, M 23.0, 95% on ART	Age/5 y: IRR 1.16 (1.10-1.21) Glucose \geq 141/100 nonfasting/fasting: IRR 12.89 (10.43-15.92) Trig 150-200: IRR 1.87 (1.34-2.60) Trig 200-500: IRR 2.91 (2.23-3.79) Trig \geq 500: IRR 5.91 (4.23-8.27) BMI: IRR 1.10/kg/m ² (1.08-1.18) Lipodystrophy: IRR 1.27 (1.02-1.56) CD4 200-349 vs <200: IRR 0.52 (0.36-0.77) CD4 \geq 350 vs < 200: IRR 1.27 (1.02-1.56) BP \geq 130/85: IRR 1.37 (1.09-1.72)
Ledergerber, ²⁶ Switzerland (Swiss HIV Cohort Study)	6513, 2000-2006, M38	69/31, 15.5% nonwhite, M 22.5, 73% on ART	Male: IRR 2.54 (1.53-4.21) 40-49 vs <40: IRR 1.93 (1.22-3.05) 50-59 vs <40: IRR 2.29 (1.30-4.09) ≥ 60 vs < 40: IRR 4.32 (2.28-8.16) Black vs white: IRR 2.10 (1.11-4.00) Asian vs white: IRR 4.88 (2.17-10.9) CDC stage C vs A/B: IRR 1.56 (1.04-2.35) Central obesity: IRR 4.69 (3.14-7.00) HCV, HTN not associated
Tripathi, ²¹ South Carolina (HIV+/HIV- matched-cohort comparison)	6816, 1994-2011, M 39	57/43, 79% nonwhite, 10% documented obese, 80% on ART	ART-treated vs HIV-neg: aHR 0.55 (0.46-0.65) ART-naive vs HIV-neg: aHR 0.82 (0.63-1.07, NS) Cumulative PI: aHR 1.35 (1.03-1.78) Female: aHR 1.32 (1.06-1.65) Age: aHR 1.09/year (1.04-1.15) HTN: aHR 2.01 (1.59-2.55) Dyslipidemia: aHR 1.71 (1.29-2.26) Obesity: aHR 1.57 (1.15-2.13) HCV not associated (aHR 1.41, 0.98-2.03)

Table 7 Tabl .: .1. C. c 1:1 with HIV (

Author	n, year(s), age	M/F, race, BMI, ART	Risk factors* (95% CI)
Butt, ²³ US (Veterans Aging Cohort Study)	3227, 2002-, A 49.6	97.5/2.5, 67% black, 10% Hispanic, 20% white, A 25.2, proportion on ART not reported	HIV: aOR 0.84 (0.72-0.97)† <i>In HIV</i> +: ART use: aOR 1.11 (1.05-1.17) NRTI/y: aOR 1.06 (1.02-1.10) NNRTI/y: aOR 1.09 (1.02-1.10) Older age (increasing with stratum) Black vs white: 1.65 (1.22-2.22) Hispanic vs white: 1.55 (1.01-2.37) Higher BMI (increasing with stratum) HCV: aOR 1.36 (1.06-1.73)

Table 3. Independent risk factors for new-onset or prevalent diabetes in people with HIV (continued)

* Only independently associated variables listed.

† Adjusted odds ratios for prevalent diabetes, not new-onset diabetes.

A, average (mean); aHR, adjusted hazard ratio; ALT, alanine aminotransferase; aOR, adjusted odds ratio; aRH, adjusted relative hazard; aRR, adjusted relative risk; BMI, body mass index; BP, blood pressure; d4T, stavudine; ddI, didanosine; HCV, hepatitis C virus; HDL, high-density lipoprotein cholesterol; HTN, hypertension; IRR, incidence rate ratio; M, median; M/F, proportion male/female; NNRTI, nonnucleoside reverse transcriptase inhibitor; NS, not significant; NVP, nevirapine; PI protease inhibitor; RR, relative rate; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine; Trig, triglycerides; WIHS, Women's Interagency HIV Study; ZVD, zidovudine.

For the diabetes study, researchers identified 4984 Danish-born people with HIV and matched them by age and gender to 19,936 people in the general population.¹⁹ Median age in the two groups stood at 38.7, 84% were men, and 97.5% were white. Through 8 years of follow-up in the HIV group and 11.2 years in the comparison group, incidence of type 2 diabetes measured 2.7% in people with HIV and 3.6% in the control group.

From 1996 through 1998, the early years of combination ART, diabetes incidence proved significantly higher in people with HIV both before they started ART (adjusted incidence rate ratio [aIRR] 2.40, 95% CI 1.03 to 5.62) and after they started therapy (aIRR 3.24, 95% CI 1.42 to 7.39). From 1999 through 2010, diabetes incidence was 55% lower in the HIV group before ART began

(aIRR 0.45, 95% CI 0.21 to 0.96) and equivalent in the two groups after HIV-positive people started ART (aIRR 1.00, 95% CI 0.79 to 1.28).

Thus the Danish team discerned a marked shift in diabetes risk among HIV-positive people relative to the general population starting in 1999.¹⁹ What happened? One factor must be dwindling prescriptions of antiretrovirals that bollix glucose metabolism. This study also linked heightened diabetes risk to stavudine, didanosine, indinavir, and saquinavir. But that can't be the whole story because diabetes risk was higher in HIV-positive people before 1999 even if they had not started antiretrovirals. The Danish investigators noted that a large DAD analysis of HIV-positive people



charted waning diabetes risk as combination ART got safer (1999-2006).²⁴ (The DAD study also implicated stavudine and didanosine—as well as zidovudine—in diabetes risk.)

The Danish researchers suggested that in these earlier years people with HIV were generally sicker than in later years and so perhaps more prone to metabolic upheavals.¹⁹ At the same time they got treated with toxic nucleoside monotherapy and with diabetogenic drugs like pentamidine. They could have also mentioned corticosteroids, thiazides, statins, certain antipsychotics, niacin, and megestrol acetate—and among illicit drugs, opiates. The lower diabetes risk with than without HIV starting in 1999, the authors noted, could partly reflect lower obesity prevalence documented in the HIV-positive Danish population than in the general population, a finding mirrored in the United States.⁸

HIV did not emerge as a new-onset diabetes risk factor in a comparison of 222 HIV-positive and 155 HIVnegative but at-risk people in the Bronx, New York, with diabetes rates of 5% in the HIV group and 8% in the comparison group.²² New-onset diabetes or prediabetes combined proved significantly less likely with than without HIV (15% versus 26%, P = 0.038).

A 2006 WIHS analysis of 1524 women with HIV and 564 at risk for HIV infection found a new-onset diabetes rate of 1.96 per 100 person-years in HIVnegative women, slightly but nonsignificantly more than the 1.53 per 100 person-years in HIV-positive women without recent antiretroviral therapy and slightly but nonsignificantly less than in women taking a PI regimen (2.50 per 100) or women taking a non-PI regimen (2.89 per 100).²⁰

A comparison of 6816 HIV-positive adults in South Carolina matched by age, race, gender, and total months of enrollment to 6816 HIV-negative Medicaid recipients also discovered differing diabetes risks with and without HIV depending on whether the HIV group was taking antiretroviral therapy.²¹ This analysis of people in care at some point from January 1994 through December 2011 found that antiretroviral-naive people with HIV did not differ from the HIV-negative group in diabetes incidence (aHR 0.82, 95% CI 0.63 to 1.07). But people taking combination antiretroviral therapy had a 45% lower risk of new-onset diabetes than did HIV-negative controls (aHR 0.55, 95% CI 0.46 to 0.65).

Finally, analysis of diabetes prevalence in 3227 HIVpositive and 3240 HIV-negative members of the Veterans Aging Cohort Study (VACS) in care after 2002 found a significantly lower diabetes rate in the HIV group (14.9% versus 21.4%, P < 0.0001).²³ Logistic regression analysis adjusted for pertinent risk factors determined that veterans with HIV had 16% lower odds of prevalent diabetes (aOR 0.84, 95% CI 0.72 to 0.97). Most of this difference reflected lower BMI in the HIV group (43.5% with HIV overweight or obese versus 48% without HIV). Within the HIV group, however, overweight doubled the odds of prevalent diabetes (aOR 2.02, 95% CI 1.30 to 3.13) and obesity quadrupled the odds (aOR 4.10, 95% CI 2.57 to 6.53).

Together these findings suggest that in most populations studied, people with HIV run an equivalent or lower risk of diabetes than comparable cohorts without HIV—perhaps because HIV groups (especially those dominated by men) tend to be leaner than their generalpopulation counterparts, and perhaps because more routine care and monitoring of people with HIV catches rising glucose early and lets clinicians reverse or at least stall the surge. As awareness of glucose abnormalities in people with HIV grew, keener monitoring probably grew apace. Among people with HIV, though, greater weight certainly boosts diabetes risk, as discussed above^{9,10} and confirmed in other studies.^{19,21,23,25} At the same time, Todd Brown argues in the interview starting on page 18,



"HIV patients have several diabetes risk factors that HIV-uninfected patients don't have," and people with multiple classical risk factors "may be at higher risk for diabetes." Brown also notes that HIV-positive people with an undetectable viral load have residual inflammation, which can contribute to diabetes risk.

Risk with antiretrovirals and other drugs

The 2014 edition of HRSA guidelines for HIV care do not count HIV infection as a diabetes risk factor.¹ They do stress that rarely used antiretrovirals—indinavir and stavudine—induced insulin resistance in shortterm studies of healthy volunteers and that other antiretrovirals "also perturb glucose metabolism."¹ The 1994-2011 population-based comparison of people with and without HIV in South Carolina found a similar new-onset diabetes risk in antiretroviral-naive people and the HIV-negative group, a lower diabetes risk in antiretroviral-treated people with HIV than in the HIV-negative group, but a one third higher risk with cumulative PI use than in people without HIV (aHR 1.35, 95% CI 1.03 to 1.78).²¹

The latest (2013) Infectious Diseases Society of America HIV guidelines say "previously reported adverse effects" of antiretroviral therapy—including diabetes—"are much less frequent with the use of the newer agents,"²⁷ an opinion endorsed by Todd Brown in the interview starting on page 18. Indeed, a 4-week placebo-controlled

Ten Nobel Prizes for research on diabetes

In an article on diabetes history, the University of Chicago's Kenneth Polonsky notes that 10 Nobel Prizes have gone to scientists working on some aspect of diabetes:

- 1923: Frederick G. Banting, John J.R. Macleod: Discovery of insulin
- 1947: Carl F. Cori, Gerty T. Cori: Course of catalytic conversion of glycogen
- 1947: Bernardo A. Houssay: Role of hormones released by anterior pituitary lobe in sugar metabolism
- 1958: Frederick Sanger: Structure of proteins, especially insulin
- 1971: Earl W. Sutherland: Mechanisms of action of hormones
- 1977: Rosalyn Yalow: Radioimmunoassays for peptide hormones
- 1992: Edmond H. Fischer, Edwin G. Krebs: Reversible protein phosphorylation as biologic regulatory mechanism

Source: Polonsky KS. The past 200 years in diabetes. N Engl J Med. 2012;367:1332-1340.



trial of atazanavir or lopinavir/ritonavir in healthy HIVnegative adults found that neither affected insulin sensitivity.²⁸ And a 48-week comparison of first-line atazanavir/ritonavir and darunavir/ritonavir found no clinically relevant differences between these PIs in fasting glucose or insulin sensitivity.²⁹ But lopinavir/ritonavir prescribing information warns that people taking these PIs may experience new-onset or worsening diabetes mellitus. And in a recent review article, Brown and two colleagues suggest the only antiretrovirals clinicians may want to switch to manage glucose upsets are lopinavir/ ritonavir, stavudine, and zidovudine.³⁰ In light of findings on currently preferred PIs, it may be time for HSRA HIV guidelines to reconsider the blanket caveat that PIs raise diabetes risk.¹

Two studies in people with HIV have linked efavirenz to abnormal glucose,^{31,32} although the impact was small (4 mg/dL).³¹ In the Veterans Aging Cohort Study, every year of nonnucleoside therapy hoisted diabetes risk 9%.²³ But a 33,389-person DAD Study analysis linked nevirapine use to lower risk of new diabetes.²⁴ Prescribing information for rilpivirine, the newest nonnucleoside, does not mention insulin resistance, glucose, or diabetes.

As for current nucleosides/nucleotides, tenofovir did not affect insulin sensitivity in HIV-negative volunteers.33 Prescribing information for coformulated tenofovir/emtricitabine (Truvada) includes no warnings on insulin resistance, glucose abnormalities, or diabetes mellitus. Elevated blood glucose is listed as a lab abnormality seen in people taking abacavir in clinical trials. But neither insulin resistance nor diabetes appears in prescribing information as an abacavir or abacavir/lamivudine (Epzicom) side effect. Alone among diabetes risk studies, a 2000-2006 WIHS analysis linked more than 1 year of lamivudine therapy to an almost tripled risk of diabetes, while finding no such association for stavudine, zidovudine, or abacavir.²⁰ Since this study also tied cumulative nucleoside use to

higher diabetes risk, longer lamivudine use could be a surrogate for longer nucleoside use.

Prescribing information for three licensed integrase inhibitors—dolutegravir, elvitegravir, and raltegravir does not list insulin resistance, glucose abnormalities, or diabetes mellitus as side effects.

Research links several non-HIV drugs to glucose abnormalities, including corticosteroids, thiazides, statins, atypical antipsychotics, niacin, and illicit opiates. Because of their wide use in people with HIV, statins deserve special attention, but research so far has yielded mixed results on how these antilipid agents affect diabetes risk. HIV/diabetes mavens Anne Monroe, Marshall Glesby, and Todd Brown note that statins can increase insulin resistance.³⁰ But "given the cardiovascular event reduction benefit from statins," they suggest, "increases in insulin resistance/diabetes mellitus likely do not outweigh the benefit of statin therapy in the general population or in HIV-infected patients."³⁰

Opiate use boosted diabetes incidence in a study of 1713 HIV-positive women and 652 HIV-negative women in the Women's Interagency HIV Study.³⁴ In an analysis adjusted for HCV infection, HIV status, antiretroviral status, and classic diabetes risk factors, current opiate use raised the risk of new-onset diabetes about 60% (aRH 1.61, 95% CI 1.02 to 2.52).

HCV: special caution warranted

Among classic diabetes risk factors tagged in HSRA HIV guidelines (**Figure 1**),¹ HCV infection merits special attention in HIV populations because of its high prevalence among HIV-positive people. The CDC figures that one quarter of HIV-positive US residents has HCV infection, and 80% of HIV-positive people who inject drugs have HCV as well.³⁵ HCV infection could add to diabetes risk by the same mechanism ascribed to HIV infection—ongoing inflammation. Unbridled inflammation spurred by untreated HCV infection could heighten diabetes risk even more. At the same time, HCV-induced liver steatosis and fibrosis—and consequent insulin resistance—could drive diabetes risk in HIV-positive people, NIH experts Hadigan and Kattakuzhy suggest.² A study of 432 people with HIV but without HCV, Hadigan and Kattakuzhy observe, linked fibrosis (estimated by aspartate aminotransferase to platelet ratio index, or APRI) to prevalent diabetes.³⁶

A 2008 meta-analysis of 34 studies determined that HCV infection boosts chances of diabetes compared with uninfected people in both retrospective studies (aOR 1.68, 95% CI 1.15 to 2.20) and prospective studies (aHR 1.67, 95% CI 1.28 to 2.06) (**Figure 2**).³⁷ People with HCV also had independently higher odds of diabetes than people with HBV (aOR 1.80, 95% CI 1.20 to 1.40). And in an unadjusted analysis, HCV/HIV coinfection nearly doubled the odds of diabetes compared with HIV monoinfection (OR 1.82, 95% CI 1.27 to 2.38).

Not all cohort studies tie HCV to diabetes in people with HIV. For example, the Swiss HIV Cohort Study of



6513 HIV-positive people seen in 2000-2006 linked age, race, CDC stage, and central obesity—but not HCV to new-onset diabetes.²⁶ A New York City case-control comparison of 49 HIV-positive people with diabetes and 49 without diabetes tied higher alanine aminotransferase to new-onset diabetes (aOR 1.16 per 10 units higher, 95% CI 1.03 to 1.30), but not HCV infection.²⁵ A study of 6816 South Carolina residents with HIV found a strong trend toward higher diabetes risk with HCV (aHR 1.41, 95% CI 0.98 to 2.03).²¹

An array of other studies have linked HCV to diabetes in people with HIV, including 1389 people naive to antiretroviral therapy,³⁸ 1230 people taking their first antiretroviral regimen,³⁹ 3227 HIV-positive US veterans,²³ and young, lean HIV-positive people without a family history of diabetes.⁴⁰ A 2001-2008 study of 78 HIV-positive pregnant women taking a PI or nevirapine regimen tied HCV coinfection to a quadrupled risk of glucose abnormalities defined by National Diabetes Data Group criteria (aOR 4.16, 95% CI 1.22 to 14.1, P = 0.022).⁴¹ (HSRA HIV care guidelines list current pregnancy, gestational diabetes, delivery of an infant weighting more than 4.1 kg (9 lb), and polycystic ovary syndrome as diabetes risk factors.¹)



Figure 2. A 34-study meta-analysis determined that HCV infection boosted odds of diabetes by two thirds in both retrospective and prospective studies (first two cones). HCV raised odds of diabetes 80% more than hepatitis B virus (HBV) infection (third cone). In an unadjusted analysis, coinfection with HCV and HCV raised odds of diabetes 82% compared with HIV alone. (Source: White DL et al.³⁷)



Results of studies like these, and the plausible mechanisms outlined above, should heighten vigilance for insulin and glucose abnormalities in HIV-positive people coinfected with HCV.

An age-old addendum

HIV populations around the world are aging, with a growing sample of studies showing survival of antiretroviral responders who do not inject drugs approaching or reaching rates in the general population. Aging makes diabetes more likely in the general population, and it does in people with HIV. Six of the nine studies in **Table 1** identified older age as an independent diabetes risk factor. A DAD Study analysis of 16,632 people in Europe, the United States, Australia, and Argentina determined that every 5 years of age boosted diabetes incidence 16%.⁹ In a South Carolina study every *1 year* of age hoisted diabetes risk 9%.²¹ Current HRSA HIV care guidelines fail to list age as a diabetes risk factor,¹ perhaps because it is so obvious. But as HIV clinicians succeed in stewarding more of their patients into older age, they would do well to keep the obvious in mind.

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PatientGuide

Diabetes facts for people with HIV

What is diabetes?

Diabetes is a treatable disease caused by high levels of blood sugar, also called blood glucose. Prediabetes is a blood sugar level above normal but not high enough to be called diabetes. Gestational diabetes can develop when a woman is pregnant.

How common is diabetes?

Almost 1 in 10 people in the United States has diabetes. Another 1.7 million people in the United States get diabetes every year.

What are the symptoms of diabetes?

High blood glucose and diabetes often have no symptoms. Three possible symptoms that you should report to your HIV provider are (1) excessive hunger despite eating regularly, (2) excessive thirst, and (3) increased urination.

Other possible signs of diabetes are extreme fatigue, blurry vision, cuts or bruises that heal slowly, and tingling, pain, or numbness in the hands or feet.

Who is at risk of diabetes?

- People 45 and older
- Overweight or obese people
- Father, mother, brother, or sister with diabetes
- Nonwhite race (see chart)
- High blood pressure
- High cholesterol or triglycerides
- Physical inactivity
- Heart disease

Sources:

Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;58:e1-e34. *http://cid.oxfordjournals.org/content/58/1/e1.long* American Diabetes Association. Diabetes basics.

http://www.diabetes.org/diabetes-basics/

What can I do to prevent or control diabetes?

- Be physically active every day
- Lose weight if you are overweight
- Get diet advice from a dietician recommended by your HIV provider
- Lower salt and alcohol intake
- Talk to your provider about lowering high blood pressure
- Talk to your provider about lowering high cholesterol or triglycerides

Should I get tested for diabetes?

Everyone with HIV infection should get tested for diabetes every 6 to 12 months.

How is diabetes treated?

If the steps outlined above do not lower high blood sugar, your provider can prescribe medications that can control prediabetes or diabetes.



* Includes American Indians and Alaska natives. Source: American Diabetes Association. Statistics about diabetes. http://www.diabetes.org/diabetes-basics/statistics/

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). National Diabetes Information Clearinghouse (NDIC). Your guide to diabetes: type 1 and type 2. *http://diabetes.niddk.nib.gov/dm/pubs/type1and2/index.aspx* US Department of Health and Human Services Health Resources and Services Administration. Guide for HIV/AIDS clinical care. April 2014. *http://aidsetc.org/guide/contents*



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