



DPAC

Diabetes Partners in Action Coalition

Providing Statewide Leadership in Diabetes Support



HEALTH DIVISION

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Diabetes and Tuberculosis

At the Crossroads of Chronic
and Communicable

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I have no financial disclosures or conflict of interest related to this presentation.

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Objectives

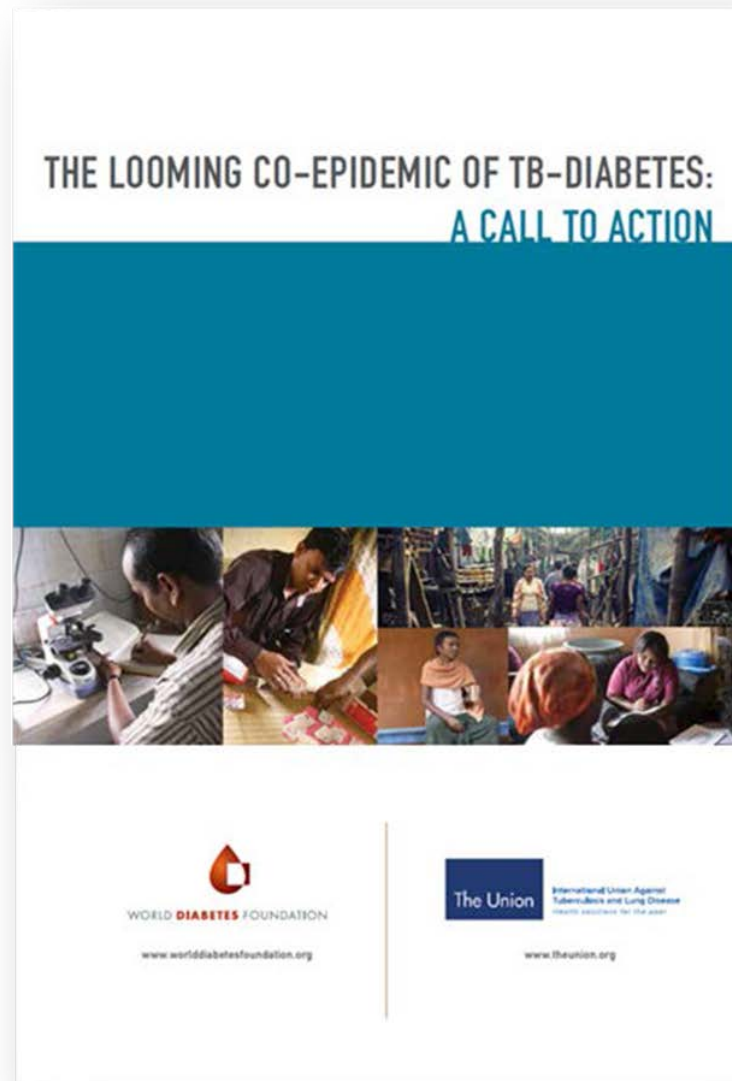
- Recognize the importance of diabetes (DM) status in patients presenting with tuberculosis (TB) infection, and conversely, recognize the importance of screening for TB in a patient with DM who has symptoms not responding to first line antibiotics for community acquired respiratory disease
- Increase awareness of treatment concerns if latent disease progresses to active disease in people with DM
- Show how implementation of screening for DM can be implemented at low cost in populous but low burden county

Definitions

- Latent tuberculosis infection (LTBI)
 - Persons are infected with *M. tuberculosis*, but do not have active TB disease.
 - Can be treated with one antibiotic
 - Not infectious
- Active TB disease
 - Persons infected with *M. tuberculosis* bacteria that progress from LTBI to symptomatic or infectious disease
 - Must be treated with multiple antibiotics

“That tuberculosis and diabetes represent two of the greatest global health challenges of our time, and their convergence globally represents a looming co-epidemic, And to this effect, we HEREBY AGREE:

To undertake action in our various capacities to support efforts to address the looming TB-diabetes co-epidemic as a public health priority”



Old Foes

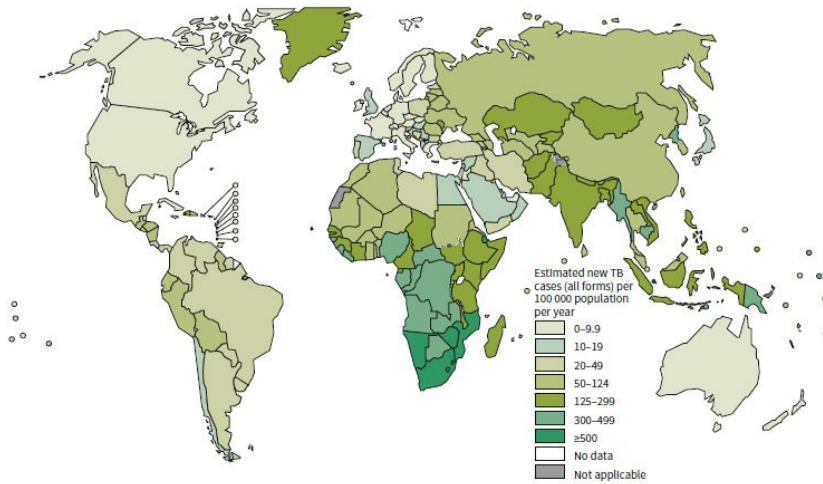
- Prior to the development of insulin in 1922 for treatment, DM was a death sentence
- Number one cause of death: Tuberculosis
- DM is also emerging as one of the most common predisposing factors for the development of active tuberculosis

The hopeless prognosis of the disease prompted Hippocrates to warn physicians to keep away from TB patients so as to preserve their professional reputation.

*"Of Animalcula, Phthisis and Scrofula
Historical insights into tuberculosis in the pre-Koch era"
Ritu Lakhtakia*

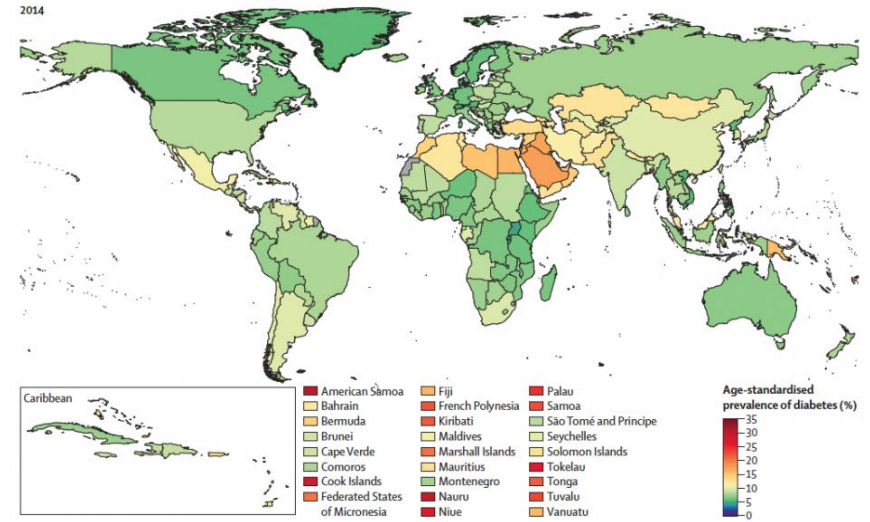
Tuberculosis Incidence

Estimated TB incidence rates, 2013



Diabetes Incidence

2014



China
India
Russia
Brazil
Indonesia
Pakistan

Diabetes Potentiates TB

- Causes relative immunocompromise
- Decrease in macrophage and lymphocyte function, leading to decreased ability to contain the organism
- Produces local tissue acidosis and electrolyte imbalance that impairs repair
- Disturbed protein metabolism with subsequent decrease of antibody formation
- Disturbed fat metabolism leading to:
 - Ketosis which decreases bactericidal effect of lactic acid
 - Increase in glycerol in the blood that then favors growth of tubercle bacilli
- Associated hepatic insufficiency from fatty liver leads to low levels of vitamins A and D, which decrease integrity of epithelial tissue

Diabetes Rising

- Oakland County Diabetes:
 - 2004: 7.1% in Oakland County
 - 2013: 9.3% in Oakland County
- Oakland County Tuberculosis:
 - 2012: 22 cases
 - 2013: 26 cases
 - 2014: 17 cases
 - 2015: 17 cases
 - 2016: 16 cases

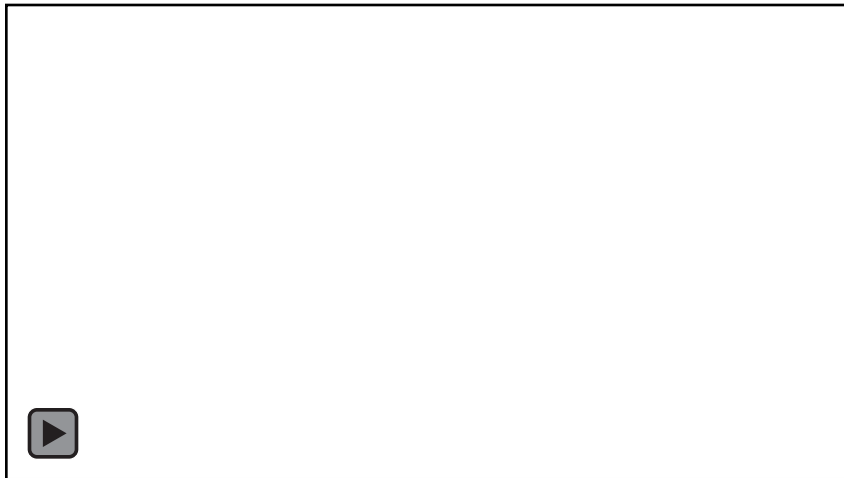
http://oakland.mi.networkofcare.org/ph/indicator_detail.aspx?id=diab_prev&c=1

http://www.michigan.gov/documents/mdhhs/2016MI_County_TUBERCULOSIS_CASES_5524847.pdf

How Much Does This Matter When Michigan Does Not Have Very Many Tuberculosis Cases?

- 3x risk of progression to active TB disease
- 2x risk of remaining culture positive
- 4x risk of relapse after standard treatment
- 5x risk of death during TB treatment

88 y.o. Woman with DM, Chronic Cough and LLL Consolidation



- From India, moved to US in 1940's
- Last TST was 20 years ago and was negative
- Last visit to India was 18 years ago
- Dry cough for 10 years
- LLL consolidation and small left pleural effusion seen on previous CXRs for at least 5 months
- At some point in those months, developed wheezing and stridor
- Treated with multiple courses of antibiotics, after diagnosis of pneumonia

Radiographic Differences For TB in Persons With Diabetes

- Seen more frequently in older patients
- Lower-lung involvement
 - Misdiagnosed as community acquired pneumonia or cancer
 - Less likely to have positive sputum smears or cultures
- Bilateral pulmonary involvement
- Multilobar disease or multiple cavities
- Radiographic abnormalities were more common in patients with poorer glycemic control
- Lower lobe involvement with cavitation should raise the possibility of co-existing diabetes
- CTs did not show statistically significant differences depending on the duration of the DM

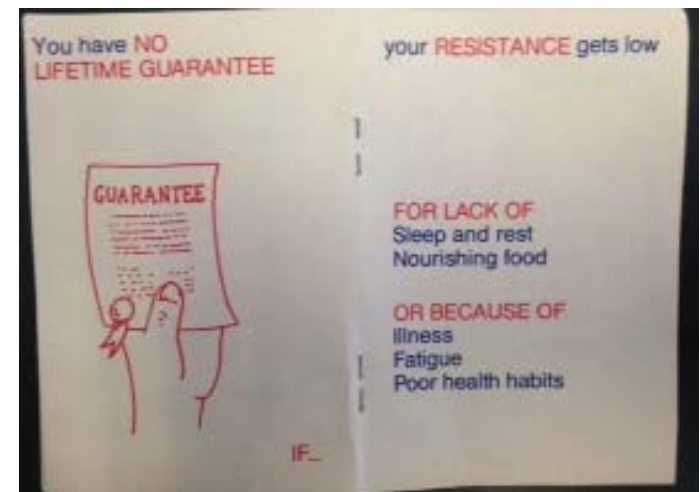
Difficulty with TB Medications

- Prior to beginning TB meds:
 - HbA1c 7.3
 - AST 18
 - ALT 14
 - Total Bili 0.3
- Within 7 days, Pt had developed nausea
 - AST 404
 - ALT 267
 - Total Bili 0.5
 - Held meds and restarted gradually
- Patient still complaining of abdominal pain– sent to ED:
 - Glucose 322
 - AST 40
 - ALT 65
 - Total Bili 0.6
- Normal to mildly elevated enzymes continued throughout treatment, as well as abdominal discomfort

*Note: Patient admitted and was given acetaminophen on floor. LFTs climbed to over 100, but return to normal when stopped

Treatment Concerns In Patients with DM and TB

- Optimum treatment is not known
- Why are the statistics so much worse for patients with DM?
 - More extensive TB disease?
 - Altered immune response?
 - Reduced concentrations of anti-TB drugs?
- Unclear what role optimum glucose control can do to mitigate negative effects of TB and DM
- TB patients with DM, are more likely to have sputum with AFB on microscopy




Managing Drug Interactions

- Pharmacokinetic factors include:
 - effects on absorption
 - metabolic pathways
 - drug transport through membranes
 - protein binding
- Pharmacodynamic interactions include:
 - synergistic or additive effects with other drugs
- Monitoring of liver and kidney functions because of increased likelihood of toxic effects of drugs


Rifampin, TB and DM

- Rifampin is a potent CYP450 inducer which lowers serum levels of sulphonylureas
- Rifampin directly causes early-phase hyperglycemia with associated hyperinsulinemia even in non-diabetics
- Insulin and Metformin preferred drugs to treat DM while on Rifampin

A total of **710 drugs** (3959 brand and generic names) are known to interact with **rifampin**.

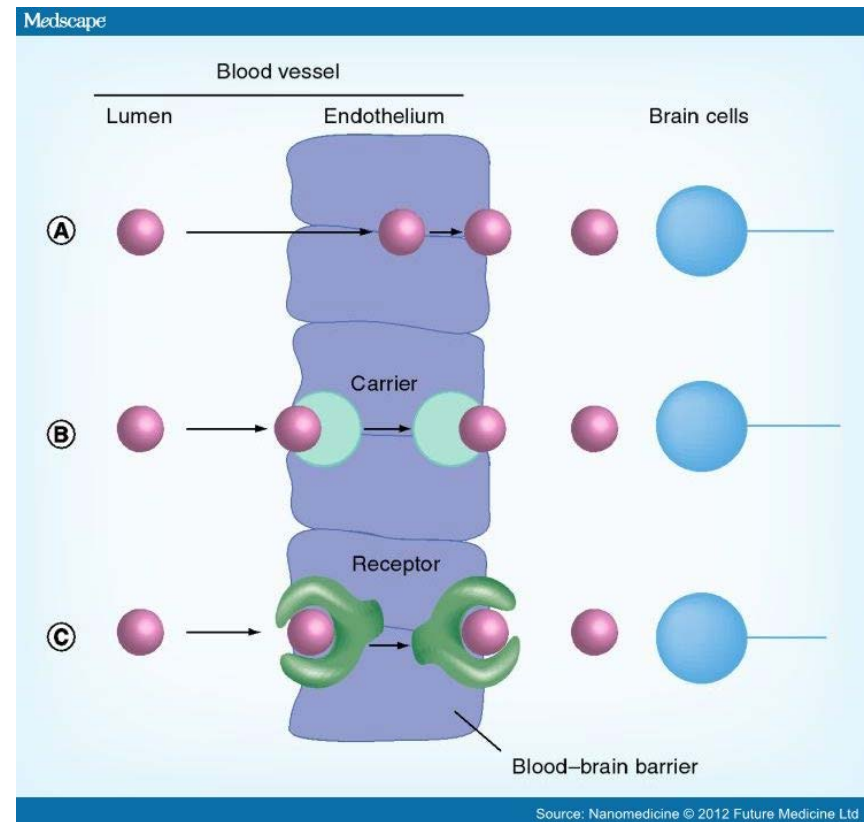
 **208 major** drug interactions (1103 brand and generic names)

 **335 moderate** drug interactions (1564 brand and generic names)

 **167 minor** drug interactions (1292 brand and generic names)

Methadone, TB and DM

- Metabolized mainly by Cytochrome (CYP) P450, but others as well
- It seems to be the only opioid that is also a CYP inhibitor
- Rifampin is the most powerful known inducer of the hepatic cytochrome P450 enzyme system
- Induction of CYP 3A4/5/7 by rifampin will increase metabolism of methadone and thus reduce its efficacy



Our Study

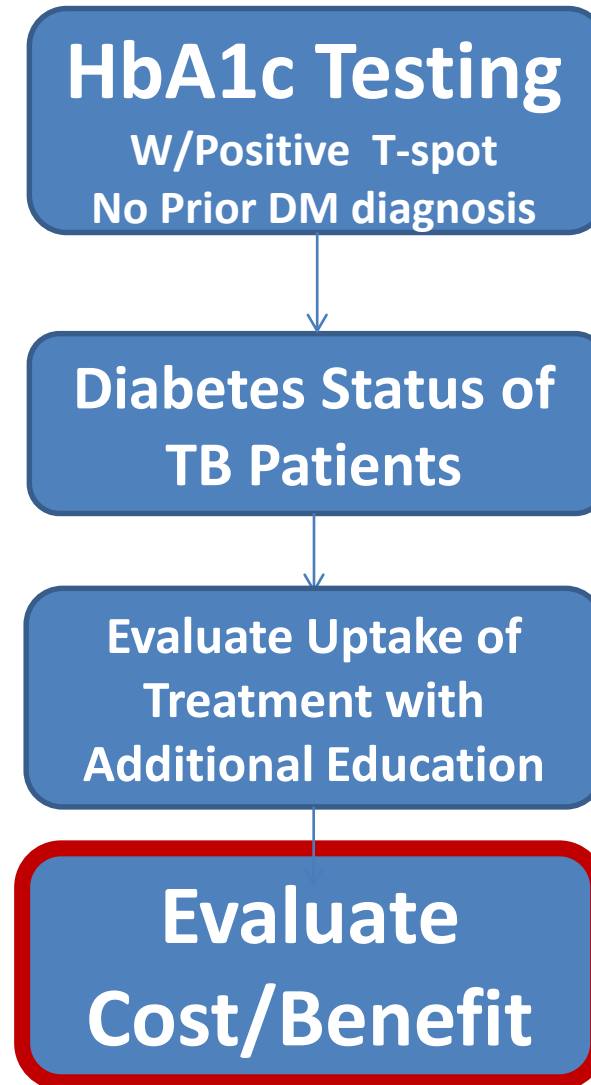


Table 1. Demographic Data and Diabetes Status of Latent and Active Tuberculosis Cases at Oakland County Health Division, 2005-2017^a

	Latent TB Cases		Active TB Cases		
	Before OCHD Testing Implemented, N (%)	HbA1c Testing, N (%)	Before OCHD Testing Implemented, N (%)	HbA1c Testing , N (%)	
Total (n=229) ^b	49 (21.40)	85 (37.12)	83 (36.24)		12 (5.24)
Demographic Information					
Age					
Mean	32.88	41.30	51.91		49.5
Sex					
Male	25 (51.02)	47 (55.29)	45 (54.22)		6 (50)
Female	23 (46.94)	38 (44.71)	38 (45.78)		6 (50)
Race/Ethnicity					
Asian	Latent TB CasesActive TB Cases				8 (66.67)
Black					1 (8.33)
White					2 (16.67)
Other					1 (8.33)
Country of Origin					
U.S.-born	Before OCHD Testing Implemented	HbA1c Testing	Before OCHD Testing Implemented	HbA1c Testing	2 (16.67)
Foreign-born					7 (58.33)
BMI					
Mean	Mean Age	32.88	41.30	51.91	49.5
Diabetes Information					
DM Status					
No DM	41 (87.23)	55 (67.07)	64 (78.05)		5 (45.45)
Prediabetes	2 (4.26)	22 (26.83)	2 (2.44)		4 (36.36)
Diabetes	4 (8.51)	5 (6.10)	16 (19.51)		2 (18.18)
Glycated Hemoglobin (%)					
Cases Tested	5 (10.2)	82 (96.47)	2 (2.41)		6 (50)
Mean (%)	5.9	5.54	8.00		5.83

^a Percentages may not add up to 100 due to missing data included in calculations.

^b Percentages in this row are out of the total population (n=164), whereas all other percentages are calculated within their own column.

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Unknown	1 (2.04)	0 (0)	0 (0)	0 (0)

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Female	23 (46.94)	38 (44.71)	38 (45.78)	6 (50)
Race/Ethnicity				
Asian	28 (57.14)	28 (32.94)	43 (51.81)	8 (66.67)
Black	11 (22.45)	23 (27.06)	24 (28.92)	1 (8.33)
White	5 (10.20)	21 (24.71)	13 (15.66)	2 (16.67)
Other	3 (6.12)	10 (11.76)	2 (2.41)	1 (8.33)

Country of Origin	Latent TB Cases		Active TB Cases	
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Other	3 (6.12)	10 (11.76)	2 (2.41)	1 (8.33)
Unknown	2 (4.09)	3 (3.53)	1 (1.2)	0 (0)

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Other	3 (6.12)	10 (11.76)	2 (2.41)	1 (8.33)
Country of Origin				
U.S.-born	18 (36.73)	10 (11.76)	24 (28.92)	2 (16.67)
Foreign-born	29 (59.18)	74 (87.06)	55 (66.27)	7 (58.33)
BMI	Latent TB Cases		Active TB Cases	
Mean				
Diabetes				
DM Status				
No Diabetes				
Pre-diabetes				
Diabetes				
Glycated Hemoglobin				
Case				
Mean				
^a Percent				
^b Percent				
U.S.-born	18 (36.73)	10 (11.76)	24 (28.92)	2 (16.67)
Foreign-born	29 (59.18)	74 (87.06)	55 (66.27)	7 (58.33)
Unknown	2 (4.09)	1 (1.18)	4 (4.81)	3 (25)

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Demographic Information				
Age				
Sex				
Race				
Country of Birth				
BMI				
Diabetes screening	The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity.		B	October 2015*
Glycated Hemoglobin (%)				
Cases Tested	5 (10.2)	82 (96.47)	2 (2.41)	6 (50)
Mean (%)	5.9	5.54	8.00	5.83

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BMI Cutoff for Asians and Asian Americans	NIH BMI Cutoff	Comments
<18.5	<18.5	Your weight is below healthy range . This can put you at risk for developing many health problems. Talk to your healthcare provider about your ideal body weight.
18.5 - 22.9	18.5 - 24.9	Your weight is within healthy range . Continue exercising and eating healthfully.
23 - 26.9	25 - 29.9	Your weight is above healthy range . Your risk for developing diabetes and other chronic disease and other chronic diseases are higher. Talk to your healthcare provider about your ideal body weight and how to make healthy lifestyle changes.
≥27	≥30	Your weight is further above healthy range . It increases the risk for developing many chronic diseases such as heart disease and diabetes, and decreases overall quality of life. Talk to your healthcare provider about your ideal body weight and how to make healthy lifestyle changes.

Initial Statistical Analysis

Latent

Table of Level by Diabetes				
Level	Diabetes			Total
	Not Diabetic	Prediabetic	Diabetic	
Latent - Self Report / Medical History	41	2	4	47
	31.78	1.55	3.10	36.43
	87.23	4.26	8.51	
	42.71	8.33	44.44	
Latent - HbA1c Testing	55	22	5	82
	42.64	17.05	3.88	63.57
	67.07	26.83	6.10	
	57.29	91.67	55.56	
Total	96	24	9	129
	74.42	18.60	6.98	100.00

Fisher's Exact Test	
Table Probability (P)	0.0002
Pr <= P	0.0031

Proportions of TB cases with diabetes and prediabetes significantly differ before and after HbA1c testing in both latent and active cases

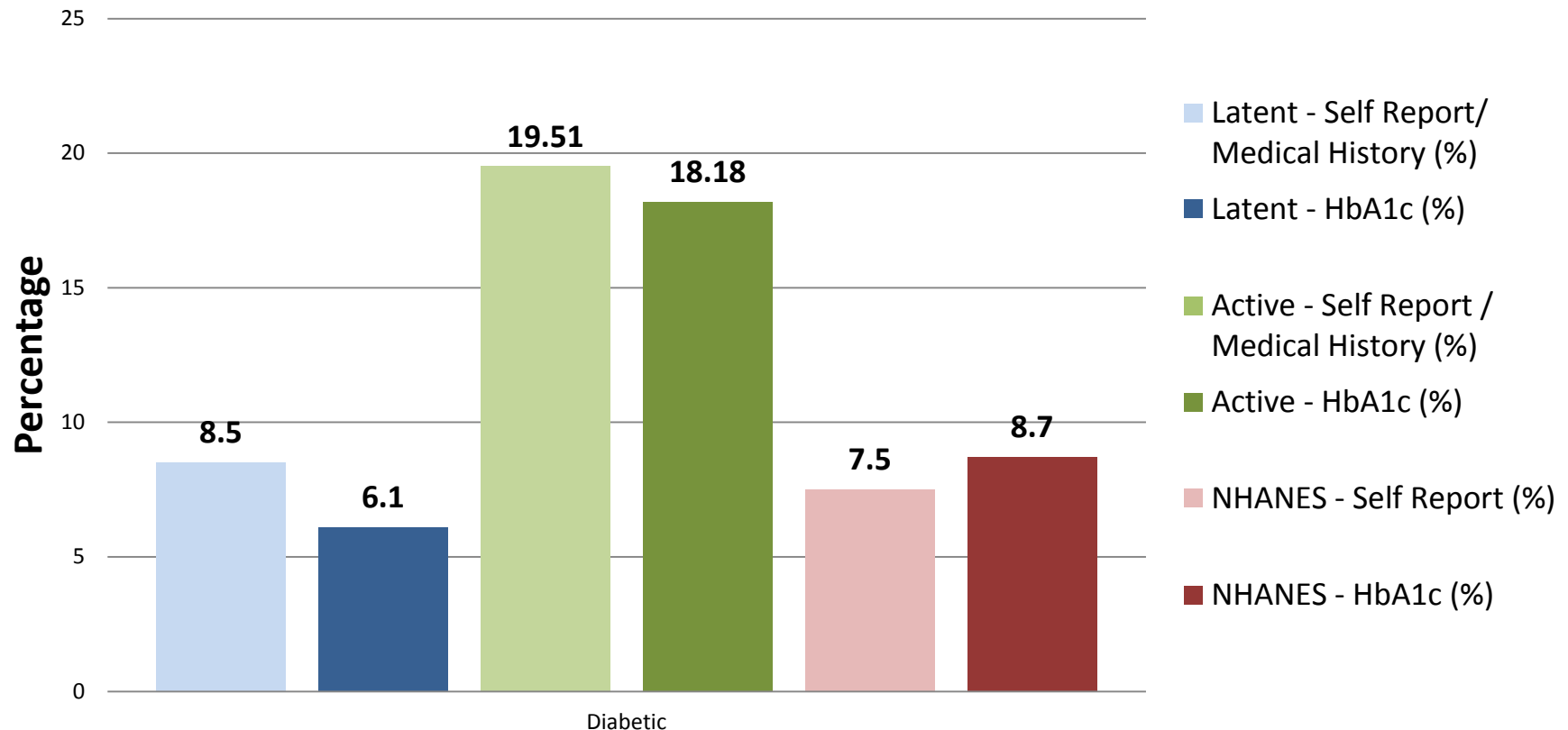
Active

Table of Level by Diabetes				
Level	Diabetes			Total
	Not Diabetic	Prediabetic	Diabetic	
Active - Self Report / Medical History	64	2	16	82
	68.82	2.15	17.20	88.17
	78.05	2.44	19.51	
	92.75	33.33	88.89	
Active - HbA1c Testing	5	4	2	11
	5.38	4.30	2.15	11.83
	45.45	36.36	18.18	
	7.25	66.67	11.11	
Total	69	6	18	93
	74.19	6.45	19.35	100.00

Fisher's Exact Test	
Table Probability (P)	0.0004
Pr <= P	0.0016

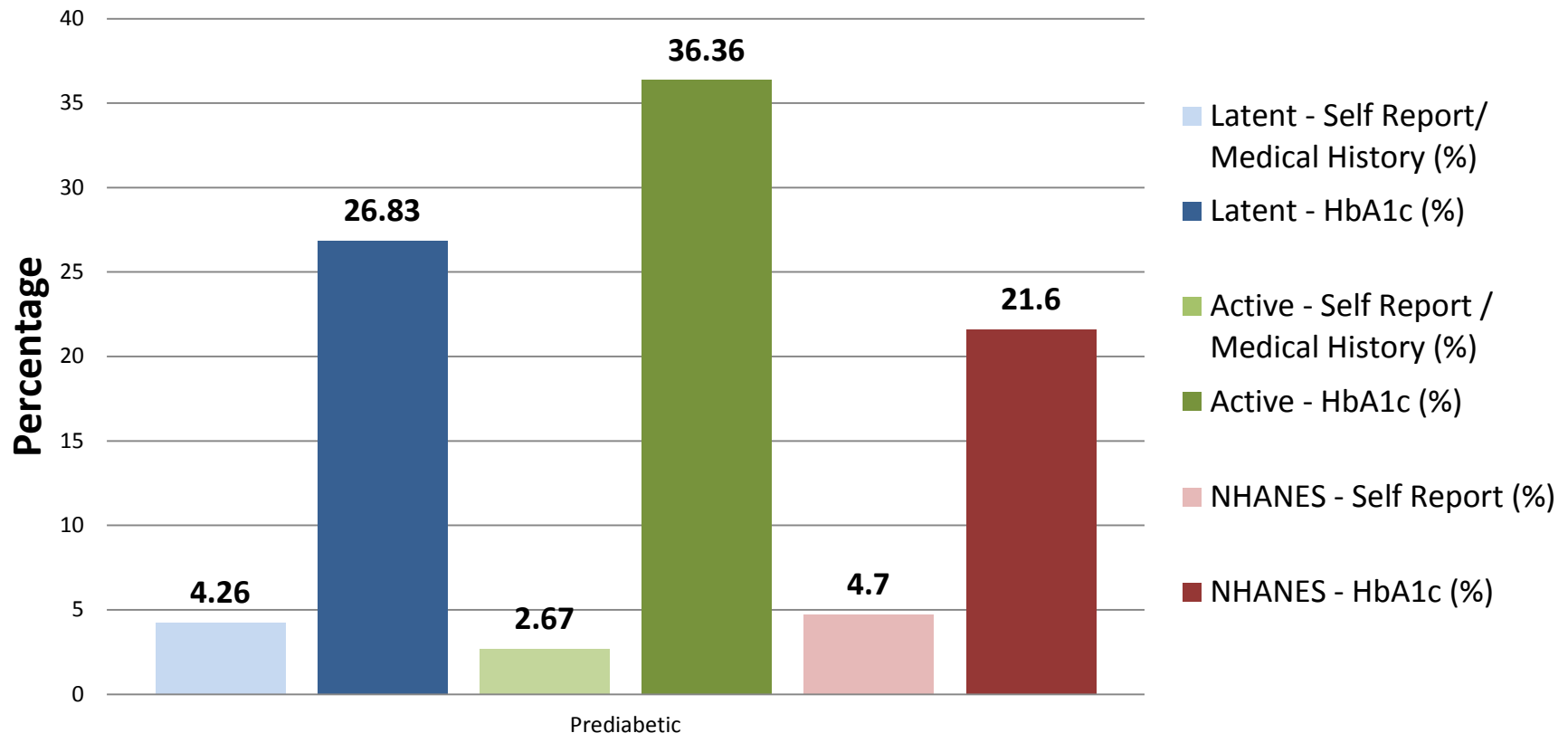
Preliminary NHANES Data For Persons With Diabetes

Known Status of Diabetes among Latent and Active TB Cases Before and After HbA1c Testing, OCHD and NHANES



Preliminary NHANES Data For Persons With Prediabetes

Known Status of Prediabetes among Latent and Active TB Cases Before and After HbA1c Testing, OCHD and NHANES



Concerns About Our Screening Program

- TB as a chronic infectious disease, may elevate blood glucose or HbA1c levels, resulting in false-positive diagnosis of diabetes.
- While we do use HbA1c, we use it as a screening test. Patients who have elevated levels are not diagnosed with DM, but simply referred to their PCP, and we check a baseline metabolic panel and then draw monthly LFTs.
 - Our initial purpose to implement HbA1c screening was to see if persons whose HbA1c indicate prediabetes could be given more intense counseling as to the benefits of taking medicine at LTBI stage
 - We also believe that it can be beneficial to potential identify active cases who present atypically

Next Steps

- Concentrations of isoniazid and rifampin below the expected range are commonly found in TB patients with DM.
- Recent study In Virginia:
 - Drug concentrations are checked in active cases after 14 daily doses of treatment.
 - 76% of all diabetics had peak concentrations of isoniazid, rifampin or both, below the expected range
 - This was then corrected with a single dose increase
 - The only significant predictor was diabetes
- Difficult to get drug levels for therapeutic drug monitoring
- New testing methods are coming

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