TB & Comorbidities

Megan Devine, MD

September 14

TB Intensive
September 13 – 15, 2023
Richmond, TX

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Megan Devine, MD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

2

Tuberculosis and Co-Morbid Conditions

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Global Impact of Co-Morbid Conditions on TB cases

TABLE 7.2
TB cases attributable to selected risk factors

RISK FACTOR	RELATIVE RISK[a]	EXPOSED (MILLIONS IN 2015)	GLOBAL POPULATION ATTRIBUTABLE FRACTION (%)	ATTRIBUTABLE TB CASES (MILLIONS IN 2015)
Undernourishment	3.1 – 3.3	734	18	1.9
HIV infection	22	36	9.4	1.0
Smoking	1.6 – 2.5	1047	7.9	0.83
Diabetes	2.3 – 4.3	460	7.5	0.79
Harmful use of alcohol	1.9 – 4.6	407	4.7	0.49

[a] Source: Lönnroth K, Castro KG, Chakaya JM et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. Lancet. 2010 May 22;375(9728):1814–29. The relative risk for HIV infection is based on data from UNAIDS and estimates from this Global TB report.

WHO Global Tuberculosis Report 2017

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TB and Co-Morbidities Closer to Home

	Diabetes	HIV	IVDU	Non-injecting drug use	Excessive Alcohol
US	16.5%	5.6%	1.3%	6.8%	10%
Texas	19%	6%	2%	9%	15%
Region 4/5N	14.8%	3.7%	0	7.4%	18.5%

2016 REPORTED TUBERCULOSIS IN THE UNITED STATES
Texas TB Surveillance Report 2016
Region 4/5 data provided by:
Daniele Fedonni and Jie Deng
DSHS TBHIVSTDdata

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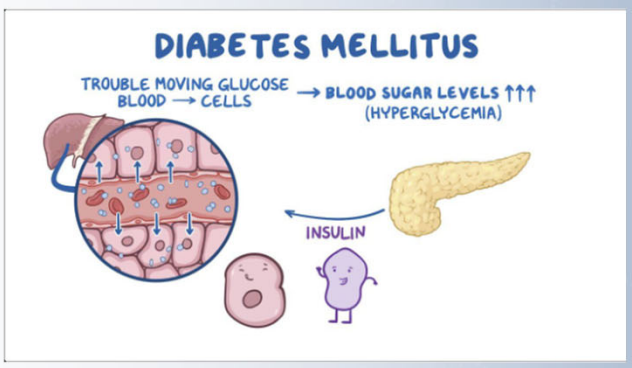

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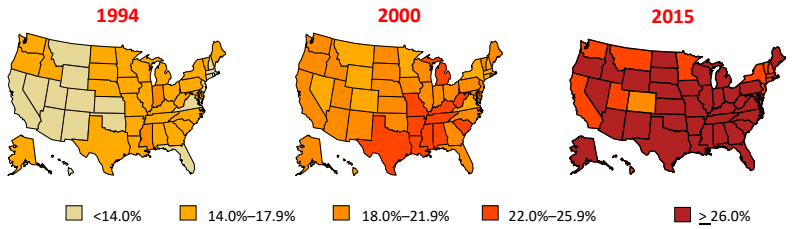
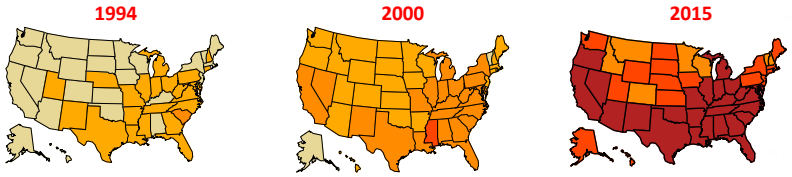
The Fattening and Sweetening of the US

Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI ≥30 kg/m²)



Diabetes



CDC's Division of Diabetes Translation. United States Surveillance System available at http://www.cdc.gov/diabetes/data

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Type 2 Diabetes in the US

- **Prevalence:** In 2015, 30.3 million Americans, or 9.4% of the population, had diabetes.
  - Approximately 1.25 million American children and adults have type 1 diabetes.
- **Undiagnosed**: Of the 30.3 million adults with diabetes
  - 23.1 million were diagnosed
  - 7.2 million were undiagnosed
- **New Cases**: 1.5 million Americans are diagnosed with diabetes every year.
- **Deaths**: Diabetes remains the 7th leading cause of death in the United States in 2015

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INT J TUBERC LUNG DIS 20(1):71–78

http://dx.doi.org/10.5588/ijtld.15.0457

Increased risk of latent tuberculous infection among persons with pre-diabetes and diabetes mellitus

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*School of Medicine, Emory University, Atlanta, †Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, ‡DeKalb County Board of Health, Decatur, §Departments of Epidemiology and Global Health, Emory Rollins School of Public Health, Atlanta, ¶Division of Epidemiology and Biostatistics, Georgia State University, School of Public Health, Atlanta, Georgia, USA

SUMMARY

SETTING: Although diabetes mellitus (DM) is an established risk factor for active tuberculosis (TB) disease, little is known about the association between pre-DM, DM, and latent tuberculous infection (LTBI).

OBJECTIVE: To estimate the association between DM and LTBI.

DESIGN: We conducted a cross-sectional study among recently arrived refugees seen at a health clinic in Atlanta, GA, USA, between 2013 and 2014. Patients were screened for DM using glycosylated-hemoglobin (HbA1c), and for LTBI using the QuantiFERON®-TB (QFT) test. HbA1c and QFT results, demographic information, and medical history were abstracted from patient charts.

RESULTS: Among 702 included patients, 681 (97.0%) had HbA1c and QFT results. Overall, 54 (7.8%) patients had DM and 235 (33.8%) had pre-DM. LTBI was prevalent in 31.3% of the refugees. LTBI prevalence was significantly higher ($P < 0.01$) among patients with DM (43.4%) and pre-DM (39.1%) than in those without DM (25.9%). Refugees with DM (adjusted OR [aOR] 2.3, 95%CI 1.2–4.5) and pre-DM (aOR 1.7, 95%CI 1.1–2.4) were more likely to have LTBI than those without DM.

CONCLUSION: Refugees with DM or pre-DM from high TB burden countries were more likely to have LTBI than those without DM. Dysglycemia may impair the immune defenses involved in preventing *Mycobacterium tuberculosis* infection.

KEY WORDS: hemoglobin A1c; QuantiFERON test; refugee; vitamin D

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Relative Risk of Progressing to Active TB Disease for Diabetes:

Table 3. Relative risk* for developing active tuberculosis (TB), by selected clinical conditions

Clinical condition	Relative risk
Silicosis	30 (*37,38*)†
Diabetes mellitus	2.0–4.1 (*42–44*)
Chronic renal failure/hemodialysis	10.0–25.3 (*39–41*)
Gastrectomy	2–5 (*45–47*)
Jejunoileal bypass	27–63 (*48–49*)
Solid organ transplantation	
Renal	37 (*50*)
Cardiac	20–74 (*51,52*)
Carcinoma of head or neck	16 (*53*)

*Relative to control population; independent of tuberculin-test status.
† Numbers in parentheses are reference numbers.

CDC, ATS, IDSA: Treatment of LTBI 2000

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Association Between Diabetes Mellitus and Active Tuberculosis:

A systematic review and meta-analysis

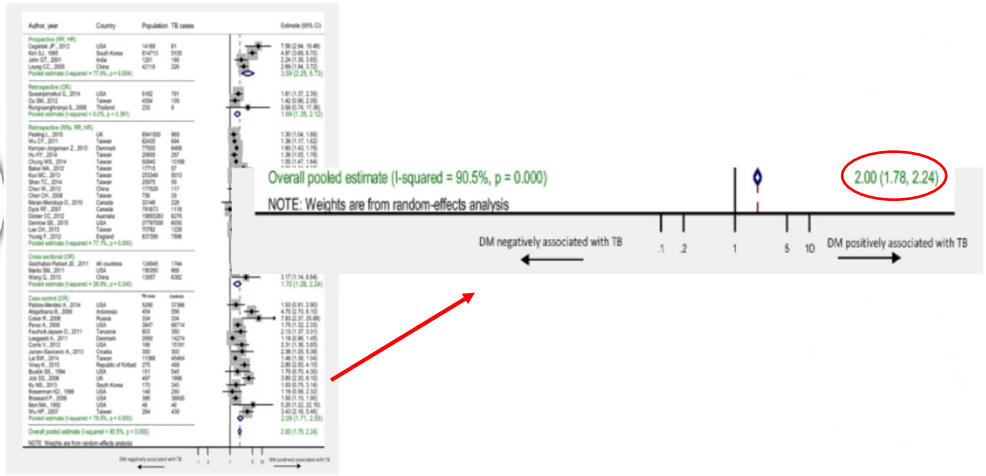

Fig 2. Forest plot of the meta-analyses. Pooled findings of 44 studies reporting adjusted estimates of the association between TB and DM, stratified according to study design. Size of the square is proportional to the precision (weight) of the study-specific effect estimates. Circle is the study–specific effect point estimate. Arrows indicate that the bars are truncated to fit the plot. The diamond is centered on the summary effect estimate, and the width indicates the corresponding 95% CI. RRs: relative risk; RR: rate ratio; OR: odds ratio; HR: hazard ratio.

Al-Rifai et al. PLoS ONE 2017 12(11): e0187967

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Association Between Diabetes Mellitus and Active Tuberculosis:

A systematic review and meta-analysis

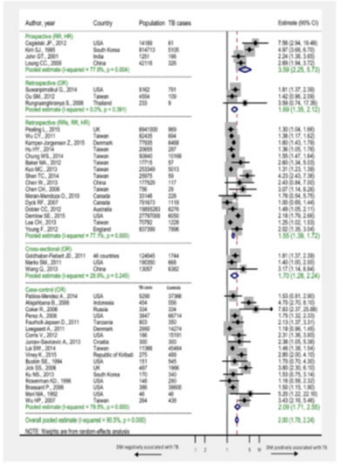

Fig 2. Forest plot of the meta-analyses. Pooled findings of 44 studies reporting adjusted estimates of the association between TB and DM, stratified according to study design. Size of the square is proportional to the precision (weight) of the study-specific effect estimates. Circle is the study–specific effect point estimate. Arrows indicate that the bars are truncated to fit the plot. The diamond is centered on the summary effect estimate, and the width indicates the corresponding 95% CI. RRs: relative risk; RR: rate ratio; OR: odds ratio; HR: hazard ratio.

Increase in risk

- By study type
  - 1.55-fold (retrospective)
  - 2.09-fold (case-control)
  - 3.59-fold (prospective)
- By country income level
  - 3.16-fold low/middle income vs. 1.73-fold in high income
- By geographical region
  - 2.44-fold in Asia
  - 1.71-fold in Europe
  - 1.73-fold in USA/Canada

Conclusion: DM is associated with a two- to four-fold increased risk of active TB

Al-Rifai et al. PLoS ONE 12(11): e0187967

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Diabetes and Clinical Presentation of TB

The New England
Journal of Medicine
VOLUME 210 JANUARY 4, 1934 NUMBER 1

THE ASSOCIATION OF DIABETES AND TUBERCULOSIS*
Epidemiology, Pathology, Treatment and Prognosis
BY HOWARD F. ROOT, M.D.†

- Autopsy series of 126 patients: no pathological findings unique to "the tubercular diabetic"
- 245 TB cases in diabetic patients, "no special insidiousness" of signs or symptoms and similar CXR findings to non-diabetics
- Did note that TB developed most frequently in patients with poor diabetic control

Dooley, & Chaisson, Lancet ID, Dec 2009

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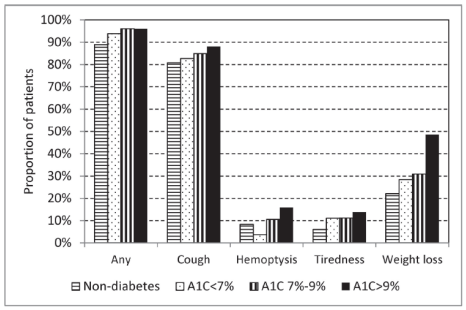
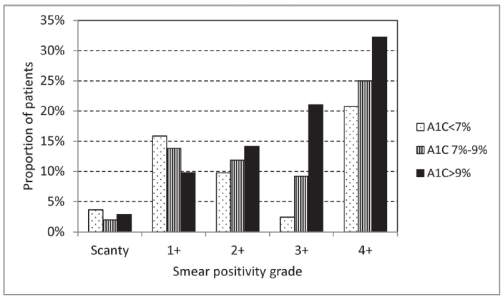
PLOS ONE

RESEARCH ARTICLE

The Influence of Diabetes, Glycemic Control, and Diabetes-Related Comorbidities on Pulmonary Tuberculosis

Chen Yuan Chiang[1,2,3], Kuan Jen Bai[2,4], Helen Ho Lin[5], Shun Tien Chien[6], Jen Jyh Lee[7], Donald A. Enarson[1], Ting-I Lee[8,9], Ming-Chih Yu[2,4]*





Chiang et al. PLoS ONE 2015 10(3): e0121698

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Does Diabetes Impact TB Treatment and Cure?

Four studies from Baltimore, Texas, Taiwan and Indonesia reveal:

- Delayed culture conversion
- Higher mortality

Dooley, 2009; Restrepo 2008; Wang 2008; Alisahlanda,2007

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Treatment Concerns – Rifampin

Rifampin induces CYP450 enzyme system increasing production of enzymes that metabolize many drugs

- Increased metabolism results in lower blood levels of drug (20 – 40+%)
- Affects many classes of diabetic medications

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Rifamycins and Anti-Diabetic Agents: Drug-Drug Interactions

General Tuberculosis (TB) Therapy Information

Developed by Kelly Bujnoch, PharmD Candidate 2011 with the assistance of Regina Tabor, RPh, DPh, Robert Petrossian and Barbara Seaworth, MD

Many diabetic medications are metabolized via the Cytochrome P450 (CYP450) enzymatic system in the liver. Rifampin is a potent inducer of the Cytochrome P450 and accounts for many of the drug interactions that occur during TB therapy.

Rifabutin is a weaker inducer of the Cytochrome P450 system, potentially interacting with some of the same medications as Rifampin.

Enzyme induction effects can last 2-4 weeks after discontinuation of rifampin. Glucose levels should be monitored and diabetic medications should be readjusted at the end of treatment.

Brand	Generic	Clinical Effect	Rifampin (RIF) Drug-Drug Interactions	Recommendations
Biguanide (Metformin) Based				
Glucophage®	Metformin	↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	None noted	No contraindications
Glucovance®	Glyburide+ Metformin	Glyburide: ↑Secretion of insulin from the pancreas Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	↓Glyburide levels 39% Metformin: None noted	•Consider glipizide as first choice sulfonylurea to minimize interactions •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy. Metformin: •No contraindications
Metaglip®	Glipizide+ Metformin	Glipizide: ↑Secretion of insulin from the pancreas Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	↓Glipizide levels 22% Metformin: None noted	
Janumet®	Sitagliptin+ Metformin	Sitagliptin: ↑Secretion of insulin from the pancreas • delays gastric emptying ↓Appetite ↓Glucagon release after meals Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	May ↓ sitagliptin levels Metformin: None noted	Sitagliptin: • Increase monitoring; interaction may be minimal and require no adjustments Metformin: •No contraindications
Sulfonylurea Based				
Micronase®	Glyburide	↑Secretion of insulin from the pancreas	↓Glyburide levels 39%	•Consider glipizide as first choice sulfonylurea to minimize interactions
Amaryl®	Glimepiride	↑Secretion of insulin from the pancreas	↓Glimepiride levels 30%	•Increase monitoring
Glucotrol®	Glipizide	↑Secretion of insulin from the pancreas	↓Glipizide levels 22%	•Consider dose adjustment of antidiabetic agents or alternative glucose control therapy.
Glucovance®	Glyburide + Metformin	Glyburide: ↑Secretion of insulin from the pancreas Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	↓Glyburide levels 39% Metformin: None noted	•Consider glipizide as first choice sulfonylurea to minimize interactions •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy. Metformin: •No contraindications
Metaglip®	Glipizide+ Metformin	↑Secretion of insulin from the pancreas Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	↓Glipizide levels 22% Metformin: None noted	
Avandaryl®	Pioglitazone + Glimepiride	Pioglitazone: ↑Insulin sensitivity (body and liver cells) Glimepiride: ↑Secretion of insulin from the pancreas	↓Pioglitazone levels 54% ↓Glimepiride levels 30%	Pioglitazone: •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy. •Consider glipizide as first choice sulfonylurea to minimize interaction Metformin: •No contraindications
Duetact®	Rosiglitazone + Glimepiride	Rosiglitazone: ↑Insulin sensitivity (body and liver cells) ↓Production of glucose by the liver ↑Cell uptake of glucose Glimepiride: ↑Secretion of insulin from the pancreas	↓Rosiglitazone levels 54-65% ↓Glimipride levels 30%	Rosiglitazone: •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy. •Consider glipizide as first choice sulfonylurea to minimize interaction Metformin: •No contraindications

Cowen Druss

Apres. 16, 2012

Heartland National TB Center Product

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TB and Diabetes -Treatment Concerns

- **Diabetic neuropathy** at baseline complicates therapy due to INH-related neuropathy
  - Baseline assessment of neuropathy
  - Vitamin B 6 (pyridoxine) to all diabetics on INH or ethionamide
- **Renal insufficiency** is associated with diabetes, especially long standing or poorly controlled diabetes
  - Adjust dose and dosing interval of EMB and PZA in those with Creatinine Cl < 30

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New Options for Treatment…..?

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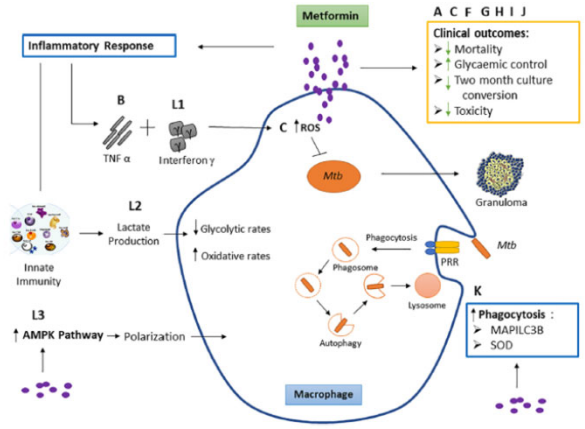
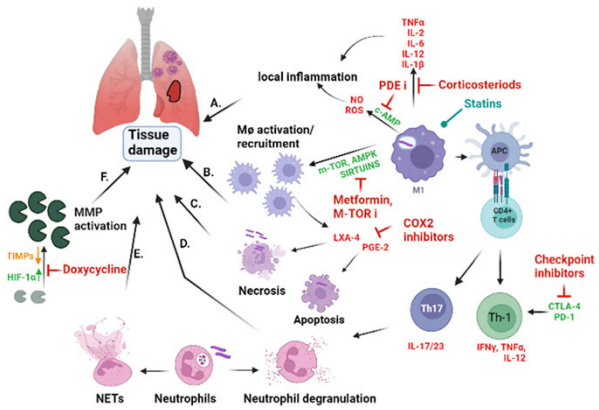
Immune Effects of Metformin



Naiker et el. Frontiers in Microbiology |April 2020 | Volume 11 | Article 435



Seminars in Immunology 65 (2023) 101672

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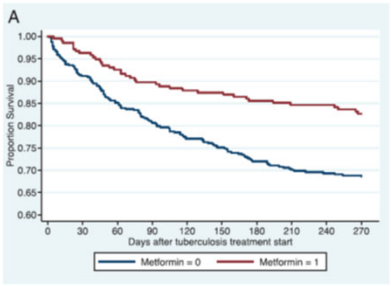
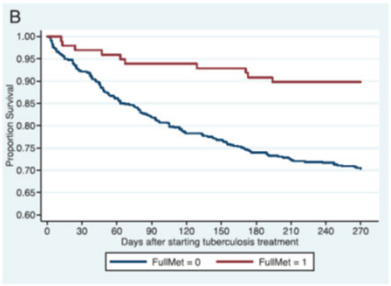
Metformin Use Reverses the Increased Mortality Associated With Diabetes Mellitus During Tuberculosis Treatment





	Metformin (n=216)	Non-Metformin (n=418)	Total (n=634)	Log-Rank χ2
Death during tuberculosis treatment -%	17.6	31.3	26.7	<0.001

	Metformin (n=219)	Non-Metformin (n=358)	Total (n=577)	Log-Rank χ2
Death during tuberculosis treatment -%	10.2	29.7	26.7	<0.001

Degner et al. CID 2018; 66(2):198–205

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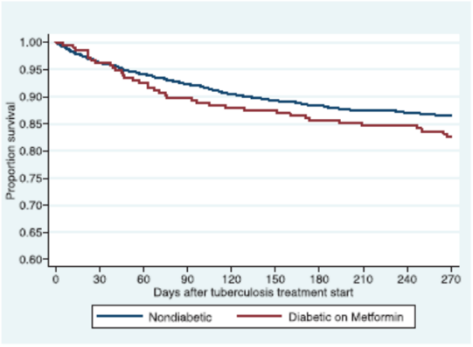
Metformin Use Reverses the Increased Mortality Associated With Diabetes Mellitus During Tuberculosis Treatment



	DM on Metformin (n=216)	Non-DM (n=1,692)	Total (n=1,908)	Log-Rank χ2
Death during tuberculosis treatment -%	17.6	13.4	13.9	0.142

Degner et al. CID 2018; 66(2):198–205

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Yu et al. BMC Infectious Diseases (2019) 19:859
https://doi.org/10.1186/s12879-019-4548-4

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review

Xinyu Yu[†1], Ling Li[†2], Liangtao Xia[1], Xin Feng[1], Fan Chen[3], Shiyi Cao[3*] and Xiang Wei[1,4,5,6*]

- Retrospective review of databases through March 2019
- 12 observational studies, 6980 cases

- Results
  - Metformin prescription was not related to lower risk of TB infection
  - Metformin prescription decreased risk of TB among diabetics (TBI to TB disease)
  - Metformin use resulted in higher probability of smear conversion at 2 months
  - Metformin medication during treatment for TB disease reduced mortality
  - Relapse was not reduced by metformin prescription

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Clinical Infectious Diseases
MAJOR ARTICLE

Randomized Trial of Metformin With Anti-Tuberculosis Drugs for Early Sputum Conversion in Adults With Pulmonary Tuberculosis

Chandrasekaran Padmapriydarsini,[1] Megha Mamulwar,[2,a] Anant Mohan,[3,a] Prema Shanmugam,[1] N. S. Gomathy,[1] Aarti Mane,[2] Urvashi B. Singh,[3] Nathella Pavankumar,[1] Abhijeet Kadam,[2] Hemanth Kumar,[1] Chandra Suresh,[1] Devaraju Reddy,[1] Poornaganga Devi,[1] P. M. Ramesh,[4] Lakshmanan Sekar,[1] Shaheed Jawahar,[1] R. K. Shandil,[1] Manjula Singh,[4] Jaykumar Menon,[5] Randeep Guleria[3]; and the METRIF Team

[1]Department of Clinical Research, Indian Council of Medical Research-National Institute for Research in Tuberculosis, Chennai, India; [2]Division of Data Management, Biostatistics and IT, Department of Clinical Research, Indian Council of Medical Research-National AIDS Research Institute, Pune, India; [3]Department of Pulmonary, Critical Care & Sleep Medicine, All India Institute for Medical Sciences, New Delhi, India; [4]Department of Thoracic Medicine, Government Ottery TB Hospital, Chennai, India; [5]Open Source Pharma Foundation, Bangalore, India; and [6]Epidemiology and Communicable Diseases, Indian Council of Medical Research, New Delhi, India

- 322 patients randomized 1:1 to RIPE vs. RIPE + metformin for 8 weeks
- All patients (not just those with diabetes)

- Results
  - Addition of metformin to ATT for 8 weeks did not hasten sputum conversion
  - Metformin did diminish excess inflammation (decreased blood cytokines), reduced lung tissue damage (seen as faster clearance on X-ray)

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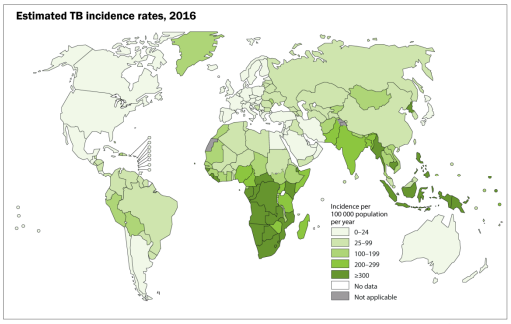
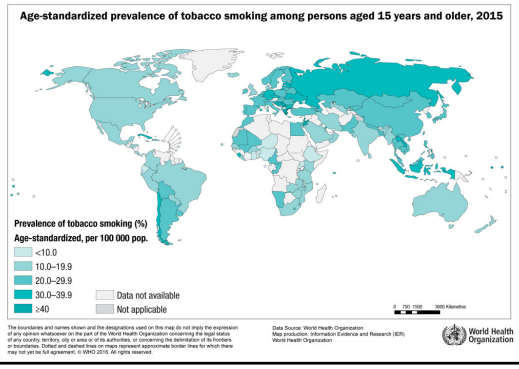
Tobacco… and TB





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Systematic Reviews and Meta-analyses Evaluating Tuberculosis and Cigarette smoking

- Slama et al, Int J Tuberc Lung Dis 2007, 11; 1049
  - "Tobacco and tuberculosis: a qualitative systematic review and meta-analysis"
- Lin et al, PLoS Med 2007, 4; e20
  - "Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis"
- Bates et al Arch Intern Med 2007
  - "Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis"
- Conclusions:
  - Smokers almost twice as likely to be infected with TB and to progress to active disease
  - 2 of 3 studies suggest smokers almost twice as likely to die from TB

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Tobacco and TB

OPEN ACCESS Freely available online PLoS MEDICINE

Tobacco Smoke, Indoor Air Pollution and Tuberculosis: A Systematic Review and Meta-Analysis

Hsien-Ho Lin[1], Majid Ezzati[2], Megan Murray[1,3,4*]

1 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America, 2 Department of Population and International Health and Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, United States of America, 3 Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital, Boston, Massachusetts, United States of America, 4 Infectious Disease Unit, Massachusetts General Hospital, Boston, Massachusetts, United States of America

January 2007 | Volume 4 | Issue 1 | e20

- Review of 33 papers on smoking and TB
- Compared with people who do not smoke, smokers have an increased risk of
  - having a positive tuberculin skin test
  - of having active TB
  - and of dying from TB
- TB control programs might benefit from a focus on interventions aimed at reducing tobacco and indoor air pollution exposures, especially among those at high risk for exposure to TB.

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Tobacco and Treatment Delay

INT J TUBERC LUNG DIS 16(6):822–827

http://dx.doi.org/10.5588/ijtld.11.0678
E-published ahead of print 9 April 2012

Longer delay in accessing treatment among current smokers with new sputum smear-positive tuberculosis in Nepal

T. S. Bam,* D. A. Enarson,† S. G. Hinderaker,‡ D. S. Bam§

*International Union Against Tuberculosis and Lung Disease (The Union), Jakarta, Indonesia; †The Union, Paris, France ‡Centre for International Health, University of Bergen, Bergen, Norway; §Kathmandu Medical College, Kathmandu University, Kathmandu, Nepal

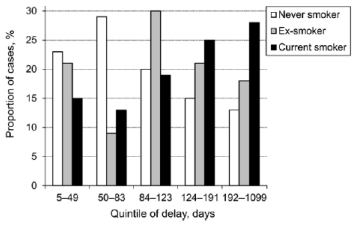

Figure 2 Association of total delay with smoking habit among new smear-positive pulmonary tuberculosis patients, Kathmandu 2006.

- 605 TB patients
  - 44.8% current smokers
  - 5.5% ex-smokers
  - 49.8% never smokers
- Median total delay in seeking treatment was 103 days
  - current smokers **133 days**
  - ex-smoker **103 days** and
  - never smokers **80 days**
- Longer delay was more common among current smokers (OR 2.03, 95%CI 1.24–3.31)

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Tobacco and Culture Conversion

INT J TUBERC LUNG DIS 17(2):225–228
©2013 The Union
http://dx.doi.org/10.5588/ijtld.12.0426

Smoking and 2-month culture conversion during anti-tuberculosis treatment

E. L. Maciel,*† A. P. Brioschi,*† R. L. Peres,* L. M. Guidoni,*† F. K. Ribeiro,* D. J. Hadad,* S. A. Vinhas,* E. Zandonade,‡ M. Palaci,* R. Dietze,* J. L. Johnson‡

*Núcleo de Doenças Infecciosas, Centro de Ciências da Saúde, Universidade Federal do Espírito Santo, Vitória, Espírito Santo, †Programa de Pós-graduação em Saúde Coletiva, Centro de Ciências da Saúde, Universidade Federal do Espírito Santo, Vitória, Espírito Santo, Brazil; ‡Tuberculosis Research Unit, Department of Medicine, Division of Infectious Diseases, Case Western Reserve University, Cleveland, Ohio, USA

- 714 patients in Brazil
- Excluded if co-morbid conditions: DM, asthma, rheumatologic disease, HIV
- 2 months daily HRZE then 2 or 4 months daily HR, all evaluated after 2 months
  - Patients who smoked had three-fold greater odds of remaining sputum culture-positive after 2 months of treatment than non-smokers
  - *Alcohol consumption did not affect culture conversion

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Tobacco and Diabetes

OPEN ACCESS Freely available online PLOS ONE

Impact of Diabetes and Smoking on Mortality in Tuberculosis

George W. Reed[1], Hongjo Choi[2], So Young Lee[2], Myungsun Lee[2], Youngran Kim[2], Hyemi Park[2], Jongseok Lee[2], Xin Zhan[4], Hyeungseok Kang[5], SooHee Hwang[5], Matthew Carroll[6], Ying Cai[6], Sang-Nae Cho[2,3], Clifton E. Barry III[6], Laura E. Via[6], Hardy Kornfeld[7]*

February 2013 | Volume 8 | Issue 2 | e58044

- 657 patients presenting at TB hospital, 25% with DM
- DM associated with greater radiographic severity and with recurrent or relapsed TB.
- Diabetes and cigarette smoking independently increased the risk of death in the first 12 months after enrollment.
- Estimating the combined impact of diabetes and smoking yielded a hazard ratio of 5.78.

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Systematic Reviews and Meta-analyses Evaluating Tuberculosis and Cigarette Smoking

- Approximately 13% of the TB cases in the world each year may be attributable to tobacco exposure.
- "Tobacco cessation must become an integral part of all TB control programs."

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Alcohol Misuse and TB

INT J TUBERC LUNG DIS 16(7):886–890
©2012 The Union
http://dx.doi.org/10.5588/ijtld.11.0624
E-published ahead of print 8 May 2012

Tuberculosis and alcohol misuse in Scotland: a population-based study using enhanced surveillance data

B. de la Haye,*† S. H. Wild,* J. Stevenson,*† F. Johnston,‡ O. Blatchford,§ I. F. Laurenson†
*Centre for Population Health Sciences, University of Edinburgh, Edinburgh, †Scottish Mycobacteria Reference Laboratory, Royal Infirmary of Edinburgh, Edinburgh, ‡Public Health Department, Lothian Health Board, Edinburgh, §Health Protection Scotland, Glasgow, UK

Table 2 Differences in disease characteristics between North Carolina tuberculosis cases reported with and without excess alcohol use

Characteristic	Excess alcohol use		
	Yes	No/unknown	
Site of disease			
Pulmonary (±extrapulmonary)	1227 (92.5%)	3266 (77.2%)	1.20 (1.17–1.23)
Extrapulmonary only	99 (7.5%)	964 (22.8%)	
Chest radiographic findings			
Cavitary	452 (36.8%)	920 (28.2%)	1.31 (1.19–1.43)
Non-cavitary	775 (63.2%)	2346 (71.8%)	
Sputum smear			
Positive	809 (65.9%)	1495 (45.8%)	1.44 (1.36–1.52)
Negative	418 (34.1%)	1771 (54.2%)	
Sputum culture			
Positive	1038 (84.6%)	2270 (69.5%)	1.22 (1.18–1.26)
Negative	189 (15.4%)	996 (30.5%)	

Chest radiographic, sputum smear, and sputum culture data are for cases with pulmonary involvement only.

Pulmonary Disease
92.3% vs 61.1%

Smear positive
74% vs 57.6%

IV drug use
4.2% vs 0.8%

Fiske et al Journal of Infection (2009) 58, 395-401

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Alcohol and Hepatotoxicity in the Treatment of TB Disease

Table 5 Dichotomous variables in cases and controls

	Cases (n=86)	Controls (n=406)	χ^2†	Odds ratio (95% CI)
High alcohol intake	19·8%	4·9%	20·4	4·76 (2·25 to 10·05)*
Extensive disease	14·0%	3·5%	13·6	4·5 (1·88 to 10·93)*
Slow acetylator	82·9%	64·2%	5·60	2·72 (1·16 to 6·57)**
Jaundice in past	11·6%	10·8%	0·001	1·08 (0·49 to 2·35)
Pyrazinamide in regimen	62·8%	25·1%	44·78	5·03 (2·99 to 8·47)***

* $p<0·001$; ** $p<0·01$; *** $p<0·1 \times 10^{-7}$.
† Yates' corrected χ^2.

Pande Thorax 1996;51:132-136

33

ORIGINAL INVESTIGATION

Tuberculosis and Substance Abuse in the United States, 1997-2006

John E. Oeltmann, PhD; J. Steve Kammerer, MBA; Eric S. Pevzner, PhD; Patrick K. Moonan, DrPH

(REPRINTED) ARCH INTERN MED/VOL 169 (NO. 2), JAN 26, 2009 WWW.ARCHINTERNMED.COM
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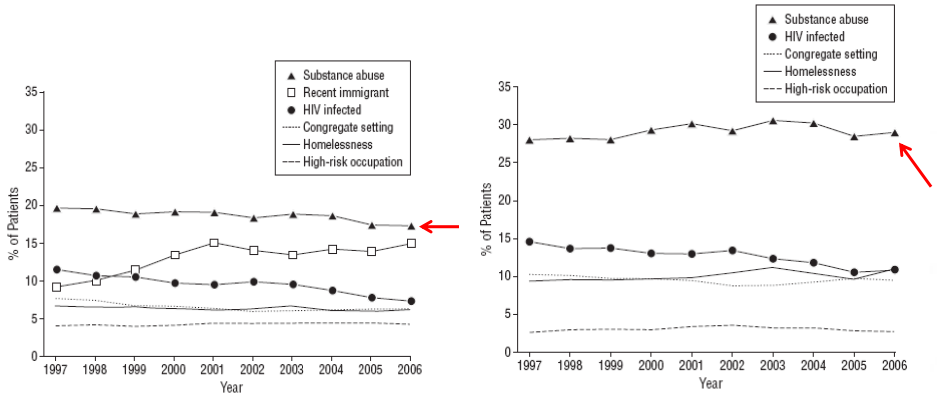
Tuberculosis and Substance Abuse in the United States, 1997-2006



Oeltmann et al. Arch Intern Med. 2009;169(2):189-197

35

Tuberculosis Outbreak Investigations in the United States, 2002–2008

Kiren Mitruka, John E. Oeltmann, Kashef Ijaz, and Maryam B. Haddad

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 3, March 2011

Table 2. Tuberculosis risk factors for patients in CDC–investigated TB outbreaks, United States, 2002–2008*

Risk factor†	No. (%) patients
Total	398 (100)
Medical	
HIV co-infection	46 (12)‡
Diabetes	23 (6)
Immunosuppression (not HIV associated)	14 (4)
History of TB	16 (4)
Incomplete treatment	7 (44)
Social	
Any substance abuse	233 (58)
Alcohol abuse	204 (51)
Nonintravenous drug use	117 (29)
Intravenous drug use	19 (5)
Incarceration history§	126 (32)
Homelessness	78 (20)

Table 3. Predominant characteristics of CDC–investigated TB outbreaks, United States, 2002–2008*

Characteristic	No. (%) outbreaks†
Total	27 (100)
US born	24 (89)
Male sex	22 (81)
Substance abuse (alcohol/drugs)	18 (67)
Acid-fast bacilli smear positive	17 (63)
Non-Hispanic black	16 (59)
Incarceration history	8 (30)
Cavitary disease on chest radiograph	7 (26)
Non-Hispanic white	4 (15)
Homelessness	4 (15)
Hispanic	3 (11)
HIV co-infection	1 (4)

*TB, tuberculosis; CDC, Centers for Disease Control and Prevention.
†Outbreak had ≥50% of patients with the select characteristic.

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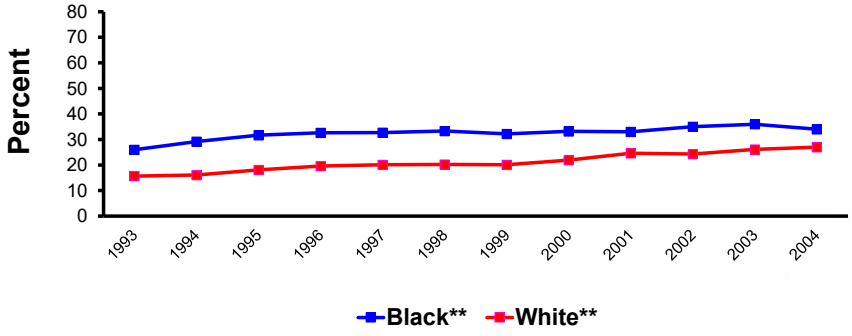
Percent of TB Cases in Persons with History of Substance Abuse,* 1993–2004



*Injecting drug, non-injecting drug, or excess alcohol use in year prior to TB diagnosis
**U.S.-born non-Hispanic

Kenneth G. Castro, MD
Stop TB in the African-American Community
May 16-17, 2006, Atlanta, Georgia

37

Substance Abuse in TB patients

- Tuberculosis Outbreak in Southern Mississippi, 2005-2007
  - Bloss et al. 2011. Southern Medical Journal 104 (11):731
  - All US-born, all HIV negative, 92% black, 82% substance abuse, 100% pulmonary disease, 170 contacts (45% TST+)
- Crack Cocaine and Infectious Tuberculosis
  - Story et al. 2008. EID 14 (9):1466
  - 64% UK-born, 64 % white or black Caribbean, crack use associated with 2.4X higher rate of smear positivity
- Tuberculosis and Drug Users in Iran
  - Shamaei et al. IJ STD & AIDS. 2009. 20:320
  - 91% Iranian, 98% men, heroin/opium, 89% sputum smear positive
- Tuberculosis Outbreak in Nevada and Arizona
  - Mitruka et al. Public Health Reports 129: 78
  - 100% Hispanic (born in Mexico), index case deported by ICE (returned), 130 contacts (54.6% TST positive), methamphetamines

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Rifampin and Opioids

- Methadone
  - Rifampin lowers the serum concentration of methadone by 33-66%
  - Administration of rifampin to patients on methadone has led to opioid withdrawal in patients on methadone replacement therapy
  - Need to increase methadone dose and monitor carefully to prevent withdrawal with co-administration of rifampin and methadone
- Codeine
  - Administration with rifampin leads to decreased biotransformation to morphine (which is responsible for most of the analgesic effects)
  - Decreased serum concentration with rifampin
- Morphine
  - 28% decrease in serum levels when given with rifampin
  - Loss of analgesic effect

Niemi et al. Clin Pharmacokinet 2003 42 (9): 819-50

39

Rifampin and Benzodiazepines

- Diazepam
  - Reduction of half-life by 76%
  - Enhanced total body clearance by 300%
  - May require a 2-3 fold increase in dose for effect
- Midazolam and Triazolam
  - Decreased serum concentration to 2-4% of controls
  - Ineffective during co-administration with rifampin

Niemi et al. Clin Pharmacokinet 2003 42 (9): 819-50

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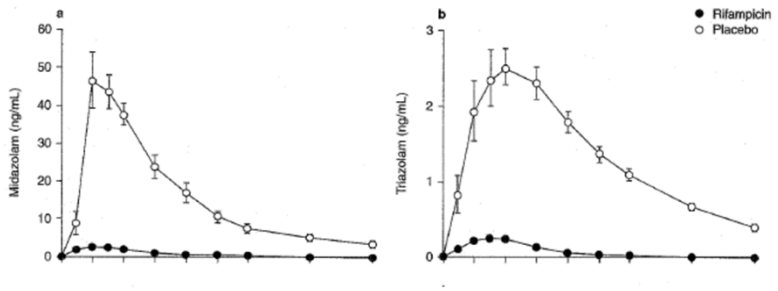
Rifampin and Benzodiazepines



Niemi et al. Clin Pharmacokinet 2003 42 (9): 819-50

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Rifampin Drug Interactions

It is imperative to be aware of all medications a patient is taking when that patient is placed on rifampin.

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Rifabutin

- A substitute for rifampin for patients who are receiving drugs, especially antiretroviral drugs, that have unacceptable interactions with rifampin.
- Adverse effects: Less severe induction of hepatic microsomal enzymes, therefore, less effect on the metabolism of other drugs

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Drug and Alcohol Dependence 118 (2011) 326–334

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

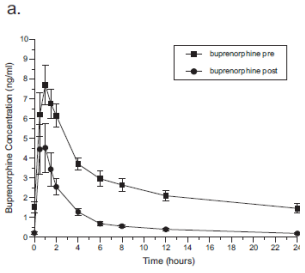
journal homepage: www.elsevier.com/locate/drugalcdep

Rifampin, but not rifabutin, may produce opiate withdrawal in buprenorphine-maintained patients

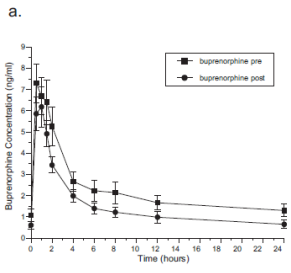
Elinore F. McCance-Katz[a,*], David E. Moody[b], Sudha Prathikanti[a], Gerald Friedland[c], Petrie M. Rainey[d]

[a] University of California San Francisco, San Francisco, CA, United States
[b] University of Utah, Salt Lake City, UT, United States
[c] Yale University School of Medicine, New Haven, CT, United States
[d] University of Washington, Seattle, WA, United States

± Rifampin



± Rifabutin



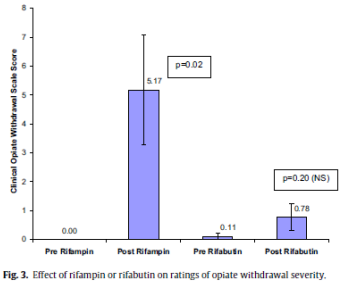


Fig. 3. Effect of rifampin or rifabutin on ratings of opiate withdrawal severity.

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Biggest Barrier to care:
What is important to you? Your patient?

- Difference in focus between care providers and substance abuser
  - Providers are focused on
    - Compliance
    - Co-morbid conditions
    - Pill counts
  - Patient is frequently focused on
    - Available foods, foods I like
    - Avoiding withdrawal
    - Avoiding drugs that make me feel bad or 'kill my buzz'
    - Next 'fix', next meal, a place to sleep
    - Avoiding incarceration

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How do we help the patient?

- Let go of stigma and focus on walking with the patient to care
- See addiction as another co-morbidity to be addressed
- Answer the question: "What's in it for me?"
  - A meal?
  - A bed?
- Explore available programs to help the patient effect a change

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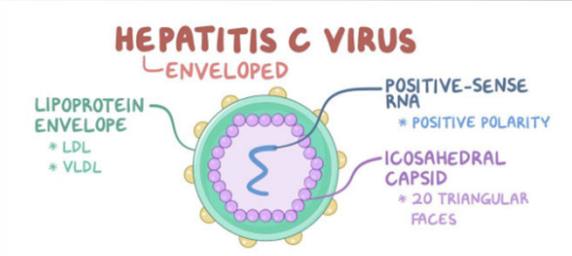
Hepatitis C – TB



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HCV and the Immune Response

HCV infection is associated with impaired macrophage activation and T-cell responses.

- Reduces production and concentration of INF-gamma and TNF alpha
  - These are involved with activation of macrophages; essential for control of MTB
- Increases level of inhibitory cytokines such as interleukin-10
  - These cytokines inhibit those cytokines needed for effective response against MTB
- Affects natural killer cells
  - Reduces their capability to produce cytokines involved in immune response pathways against MTB
- Viral persistence in chronic HCV can lead to functionally inferior T cells – T cell exhaustion
  - Leads to decreased release of inflammatory mediators including IFN-gamma

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TB - HCV

MTB

- Globally 1.7 "**billion**" infected with MTB
  - Highest prevalence Africa and Asia
- Likely over 1000 cases in Texas for 2022

HCV

- Globally - 58 **million** with chronic HCV
  - 1.5 million new cases/year
    - Highest prevalence in WHO's eastern Mediterranean and European regions
  - U.S. 2019 – 123,312 newly reported chronic cases

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Who is at risk and should be tested ?

Contacts of someone with TB

People who have lived in areas of world where TB is common

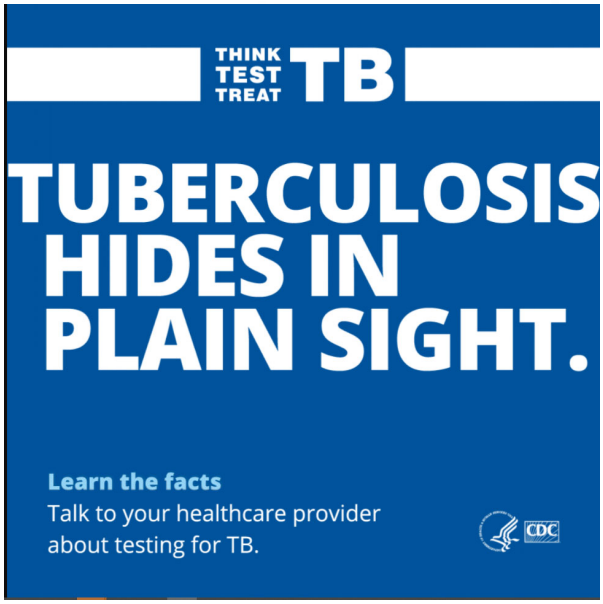
People who like or work in high-risk settings

- correctional settings
- long term care facilities
- nursing homes
- homeless shelters

Health-care workers who care for patients at increased risk of TB disease

Infants, children and adolescents exposed to adults who are at increased risk for LTBI or TB disease

Those with HCV infection????



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Risk Factors for Progression from LTBI to Active TB Disease

- Immune compromising conditions
  - HIV
  - Diabetes
  - Organ Transplantation
  - Smoking
  - Malignancy
  - Immune suppressing medications
  - Elderly
  - **Hepatitis C????**

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Clinical Infectious Diseases
MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Association of Treated and Untreated Chronic Hepatitis C With the Incidence of Active Tuberculosis Disease: A Population-Based Cohort Study

Davit Baliashvili,[1,a] Henry M. Blumberg,[1,2] David Benkeser,[3] Russell R. Kempker,[2] Shaun Shadaker,[4] Francisco Averhoff,[5] Lia Gvinjilia,[6] Natalia Adamashvili,[7] Matthew Magee,[8] George Kamkamidze,[9] Mamuka Zakalashvili,[10] Tengiz Tsertsvadze,[11] Lali Sharvadze,[12,13] Mamuka Chincharauli,[14] Nestan Tukvadze,[14] and Neel R. Gandhi[1,2,8]

January 2023

Study aim: Assess how untreated and treated chronic HCV infection status impacts the incidence of active TB disease.

Hypothesis: Incidence of active TB is highest among those with untreated chronic HCV infection followed by those who were treated and lowest among those never infected with HCV

- Conducted cohort study among adults in Georgia tested for HCV from 1/1/2015 – 9/30/2020
  - Excluded those with known diagnosis of active TB disease before or at time of first HCV test.

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Methods and Setting:

Eastern European country of Georgia

TB 70 cases/100,000 in 2020

All TB diagnostic and treatment services free

During study period only children < 5 and high-risk groups such as HIV + were offered LTBI testing and screening.

Chronic HCV infection highly prevalent in Georgia

Affects 5.4% of general adult population

First country to implement nationwide program to eliminate HC

Screening in multiple setting and free treatment

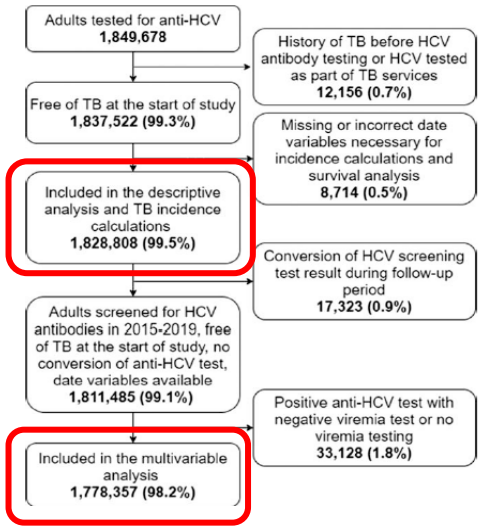

Figure 1. Flow chart of study population: persons tested for HCV antibodies, 1

Followed for median time 26 months for TB disease after screen

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Results

- Active TB diagnosed in 3136 persons during follow up
- Incidence rate/1000,000 person-years:
  - Untreated HCV – 296 **> 4 times higher than never infected**
  - Treated HCV - 109 1.7 times higher than never infected
  - HCV negative - 65
- Those treated who had sustained virologic suppression had lower rates of TB (1.5 times greater than never infected).

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Conclusions

- Adults with HCV infection, particularly untreated individuals were at high risk of developing active TB disease
- Persons with HCV infection should be screened for LTBI TB infection and active TB disease
- Suggests those who are positive be treated for LTBI
  - Safety of LTBI therapy unclear in chronic HCV

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Table 3.7. Number and rates* of deaths with hepatitis C listed as a cause of death† among residents, by state or jurisdiction — United States, 2015–2019

Print

◀ Table 3.6 | Table 3.8 ▶

Texas in top three by number of deaths but not rate

State or Jurisdiction	2015 No.	2015 Rate*	2016 No.	2016 Rate*	2017 No.	2017 Rate*	2018 No.	2018 Rate*	2019 No.	2019 Rate*
Pennsylvania	726	4.18	564	3.28	563	3.15	417	2.37	445	2.48
Rhode Island	97	7.26	89	6.57	76	5.15	91	6.37	57	3.79
South Carolina	294	4.67	299	4.51	302	4.51	259	3.7	220	3.09
South Dakota	35	3.33	37	3.46	29	2.56	30	2.8	29	2.61
Tennessee	592	7.27	482	5.89	469	5.57	517	6.01	491	5.77
Texas	1,996	6.72	1,886	6.12	1,888	6.03	1,708	5.3	1,383	4.2

CDC National Center for Health Statistics; http://wonder.cdc.gov/mcd-icd10.html

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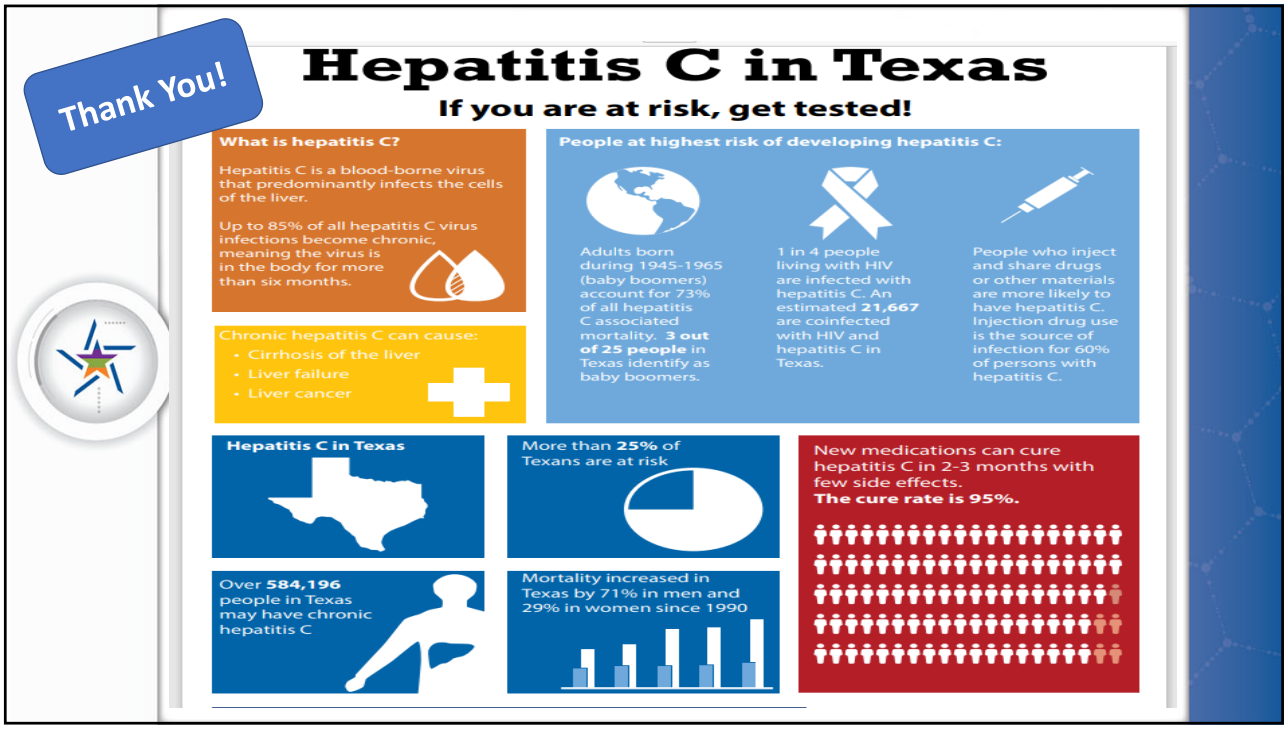

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THEY ALWAYS COME BACK

Do It Right The First Time!

Barbara Seaworth, MD

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