TB DISEASE AND COMORBIDITIES

PREGNANCY, DIABETES, HIV

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TB Nursing Symposium
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OBJECTIVES

- Analyze the impact of important comorbidities on TB disease manifestations
- Determine appropriate approach for evaluation of HIV-TB coinfection
- Identify critical issues with management of TB disease in pregnancy

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POLL OPEN

Which of the following is the most common medical risk factor for development of TB disease in the United States?

1. HIV
2. Diabetes mellitus
3. Solid organ transplant
4. Use of TNF alpha inhibitors

Which of the following is the most common medical risk factor for development of TB disease in the United States?

A. HIV

B. Diabetes mellitus

C. Solid organ transplant

D. Use of TNF alpha inhibitors

Diabetes is the most common medical risk factor for TB disease in the US

1 in 4 people with TB have diabetes

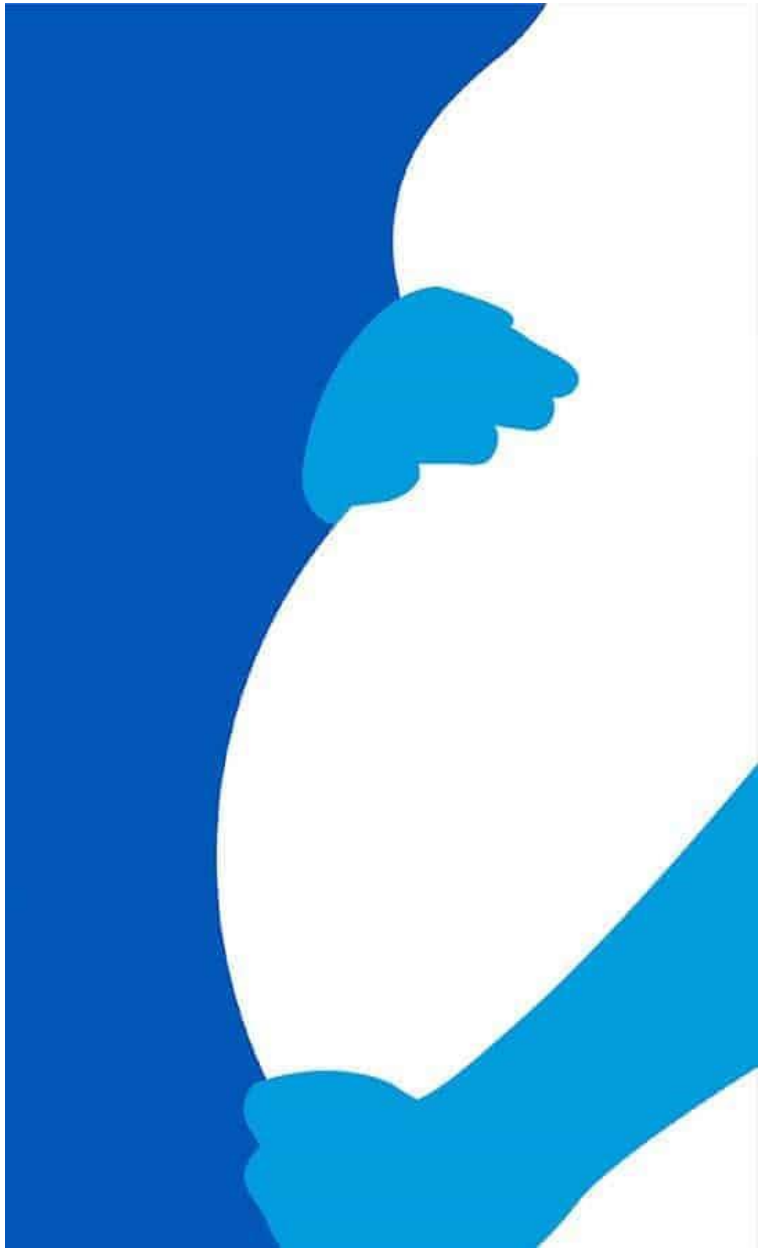
38 million people (15%) of US adults have diabetes

8 million adults are unaware they have diabetes

RISK OF TB DISEASE	
No risk factors	5% in the first 2 years after infection 10% lifetime risk
HIV	10-100 x relative risk
Organ transplant	20-70 x relative risk
TNF alpha inhibitors	1.6-25.1 x relative risk
Diabetes mellitus	1.6-7.83 x relative risk

Ai JW et al. Emerg Microbes Infect. 2016 Feb; 5(2): e10

PREGNANCY



TB IN PREGNANCY

- Higher incidence of TB diagnosis in pregnant & postpartum
- Untreated TB disease associated with adverse maternal & fetal outcomes
  - Increased maternal morbidity (hospitalization, preeclampsia, eclampsia, anemia)
  - Increased miscarriage
  - Increased preterm birth
  - Increased IUGR, SGA, low birthweight
  - Increased perinatal death
- Benefits of treatment outweigh potential risks from TB drugs

Sobhy S et al. Br J Obstet Gynaecol 2017;124:727–33. 3
Sugarman J et al. Lancet Glob Health 2014;2:e710–6

TB IN PREGNANCY

- Limited data to guide optimal management
- Need greater inclusion in research to develop robust evidence-based guidance
- Less likely to receive patient centered high quality care
- Most studies show successful TB treatment, maternal and infant outcomes

- CDC recommends screening all women at high risk of TB when establishing antenatal care
- All pregnant people should be screened for HIV

SCREENING FOR TB IN PREGNANCY

- **Symptom assessment**
  - Anorexia, weight loss, fever, night sweats, cough > 3 weeks, hemoptysis, fatigue, generalized weakness
  - TB symptoms may overlap with normal pregnancy symptoms

- **Examination** (pulmonary and extrapulmonary)

SCREENING FOR TB IN PREGNANCY

- **Assess risk factors for TB exposure**
  - Recent contact with a person with TB disease
  - Living or working in high-risk areas (healthcare settings, LTCF, nursing homes, jails/prisons, shelters etc)
  - Incarcerated
  - Unhoused
  - Immigration from or regular travel to high TB prevalence area

SCREENING FOR TB IN PREGNANCY

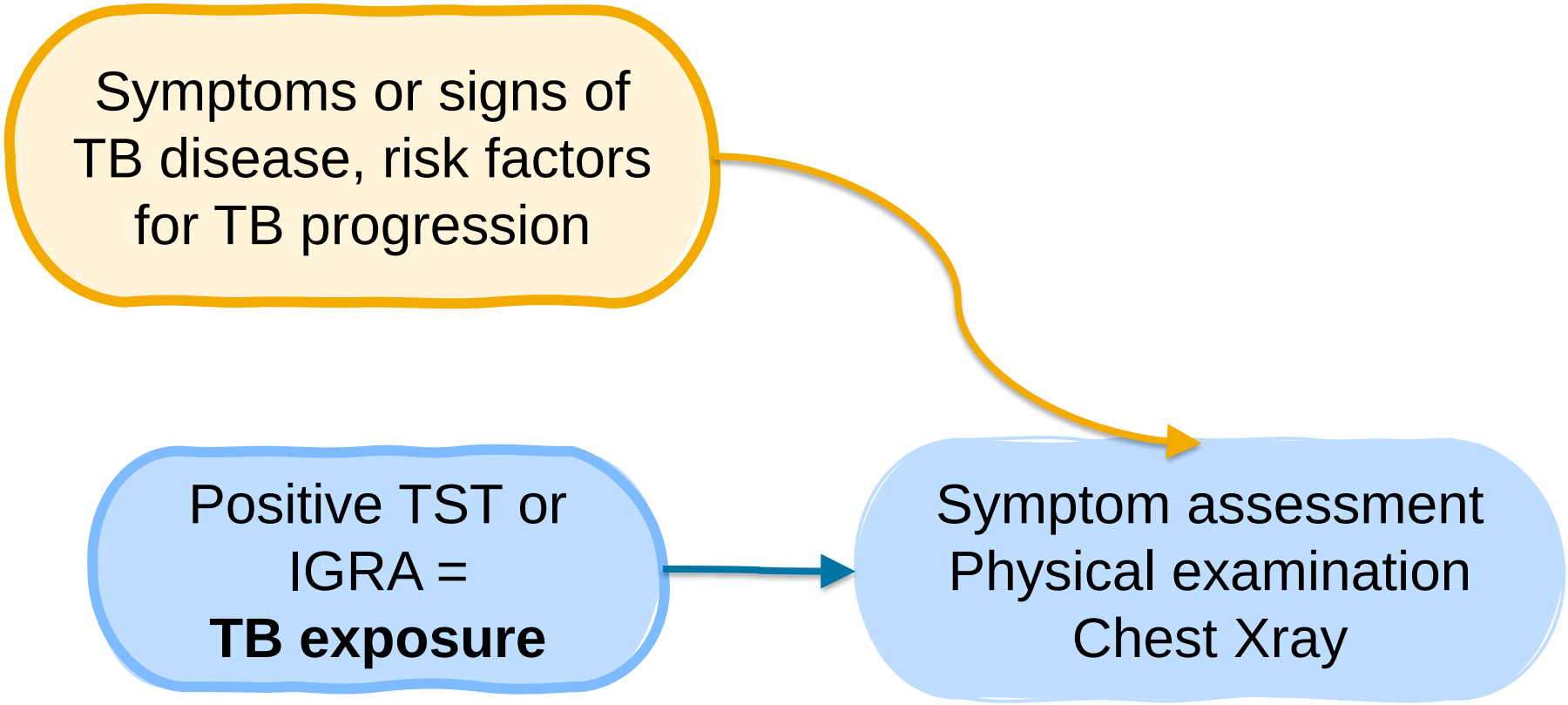
- **Assess risk of progression to TB disease**
  - HIV
  - Injection drug use
  - Immunocompromised
    - Corticosteroids
    - TNF alpha inhibitors
    - Hematologic malignancy
    - Solid organ transplant
    - Head/neck cancer
    - Other immunosuppressive therapy

Obtain TB testing (tuberculin skin test or IGRA) if TB symptoms or signs, risk factors for exposure or progression

TB TESTING

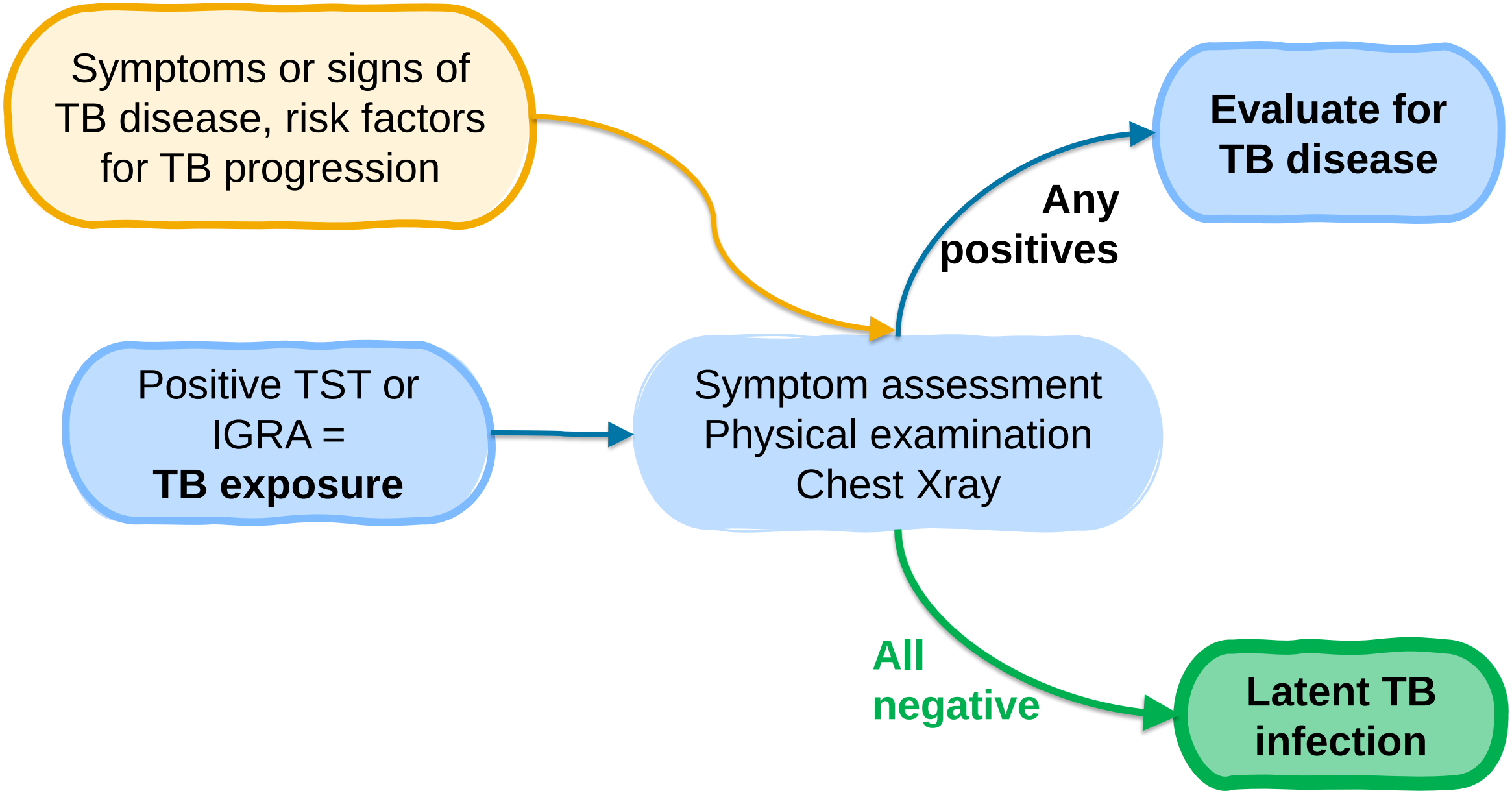
- Tuberculin skin test
  - Safe in pregnancy
  - Positive 2-12 weeks after exposure
  - False positive: Prior BCG vaccine

- IGRA
  - Preferred if prior BCG vaccine



EVALUATION FOR TB DISEASE

- Symptoms and signs
  - Same manifestations as non-pregnant
  - Presentation may be delayed, malaise may be attributed to pregnancy
- Imaging – chest x-ray
  - Pregnant people should not be denied necessary diagnostic procedures
  - CXR not associated with significant radiation to fetus (regardless of gestational age), can use shielding
- Microbiology
  - Sputum or other sites of possible involvement
  - AFB smear, mycobacterial cultures, MTB PCR



LATENT TB TREATMENT

- Shared decision making, individualize risk to pregnant person
  - Risks and benefits of LTBI treatment during pregnancy
  - Risks of progression to TB disease during pregnancy and early postpartum

- Many can defer until 2-3 months postpartum unless high risk of progression to TB disease

CDC Latent tuberculosis infection: a guide for primary health care providers

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POLL OPEN

Who should be offered latent TB treatment during pregnancy?

1. Exposure to pulmonary TB disease over 10 years ago
2. Known positive TB IGRA for over 10 years
3. ✓ Immunocompromised with recent exposure to pulmonary TB disease
4. Well controlled HIV infection without known recent exposure or TB test conversion

WHO SHOULD BE OFFERED LATENT TB TREATMENT IN PREGNANCY?

- Positive TST/IGRA in people without HIV
  - Recent exposure to pulmonary TB disease
  - TST or IGRA conversion within past 2 years
  - Immunocompromised
- Negative TST/IGRA with recent exposure to pulmonary TB disease
  - Immunocompromised
- People with HIV infection
  - Uncontrolled HIV infection
  - Recent exposure to pulmonary TB disease
  - TST or IGRA conversion within past 2 years

- Multicenter, double-blind, placebo-controlled, non-inferiority trial of 956 pregnant women with HIV
- Randomized to immediate isoniazid preventive therapy during pregnancy or deferred at week 12 after delivery
- All on ART, 67% controlled

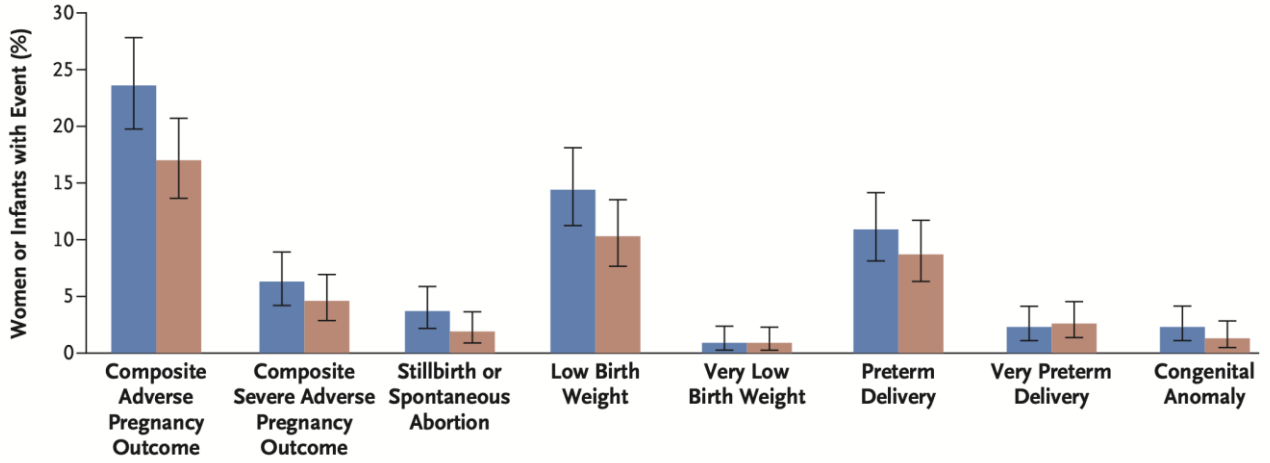
- Similar rates of TB
- Higher rates of composite adverse pregnancy outcomes in immediate group

- Deferred IPT not inferior to immediate IPT for those on ART

Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women

A. Gupta, G. Montepiedra, L. Aaron, G. Theron, K. McCarthy, S. Bradford, T. Chipato, T. Vhembo, L. Stranix-Chibanda, C. Onyango-Makumbi, G.R. Masheto, A. Violari, B.T. Mmbaga, L. Aurpibul, R. Bhosale, V. Mave, V. Rouzier, A. Hesseling, K. Shin, B. Zimmer, D. Costello, T.R. Sterling, N. Chakhtoura, P. Jean-Philippe, and A. Weinberg, for the IMPAACT P1078 TB APPRISE Study Team*

B Composite Adverse Pregnancy Outcomes and Components



No. of Events/ Total No. (%)							
Immediate treatment	106/449 (23.6)	28/448 (6.3)	17/459 (3.7)	62/430 (14.4)	4/430 (0.9)	48/442 (10.9)	10/442 (2.3)	10/440 (2.3)
Deferred treatment	78/460 (17.0)	21/458 (4.6)	9/466 (1.9)	46/446 (10.3)	4/446 (0.9)	40/458 (8.7)	12/458 (2.6)	6/458 (1.3)
RD (95% CI)	6.7 (0.8 to 11.9)	1.7 (–1.3 to 4.8)	1.8 (–0.4 to 4.1)	4.1 (–0.3 to 8.6)	0.0 (–1.5 to 1.6)	2.1 (–1.8 to 6.1)	–0.4 (–2.6 to 1.8)	1.0 (–0.9 to 3.0)
P Value	0.01	0.27	0.09	0.07	0.86	0.29	0.75	0.26

Gupta A et al. N Engl J Med. 2019 Oct 3;381(14):1333-1346

LTBI REGIMENS

4R	Rifampin daily for 4 months
3HR	Isoniazid and rifampin daily for 3 months
6H **9H**	Isoniazid daily for 6 or 9 months 9 months is preferred Consider in HIV (drug interactions)

Limited safety data for rifapentine – non-preferred in pregnancy

3HP (once weekly isoniazid & rifapentine 3 months), 1HP (daily isoniazid & rifapentine for 1 month)

CDC Latent tuberculosis infection: a guide for primary health care providers

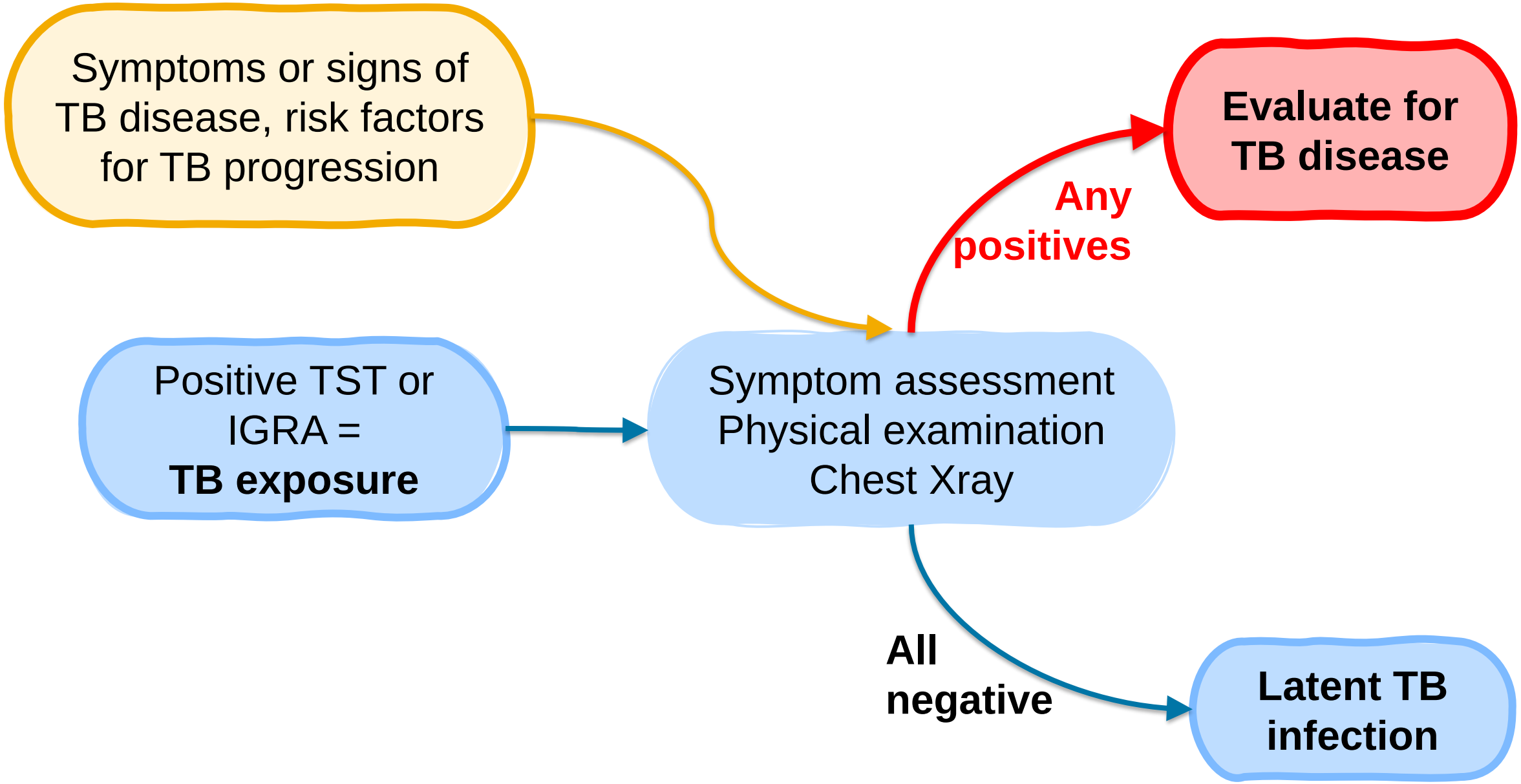
LTBI REGIMENS

- Isoniazid
  - Possible increased risk of hepatotoxicity in pregnancy and early postpartum
  - Other possible adverse effects: Rash, neuropsychiatric changes, peripheral neuropathy

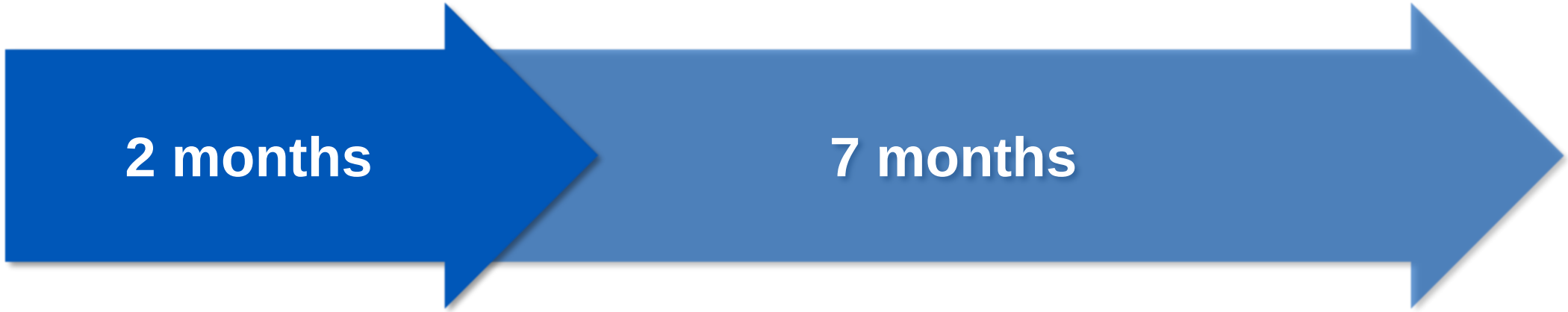
- Rifampin
  - Hepatitis, thrombocytopenia, hemolytic anemia, rash, fever

MONITORING ON LTBI TREATMENT

- Baseline
  - Liver function tests (ALT, AST, bilirubin)
  - HIV, hepatitis B (HBsAg, HBcAb, HBsAb), hepatitis C screening
  - Evaluate for chronic liver disease, alcohol, other hepatotoxins
  - Patient counselling: Anorexia, nausea/vomiting, jaundice, dark urine, rash, paresthesia, fever > 3 days, abdominal pain, bruising/bleeding
- During treatment
  - Monthly clinical symptom evaluation, examination
  - Monthly liver function tests
  - More frequent monitoring if baseline abnormal liver function tests or liver disease
- Breastfeeding is not contraindicated



DRUG SUSCEPTIBLE TB DISEASE TREATMENT



INITIAL PHASE
INH, RIF, EMB

CONTINUATION PHASE
INH, RIF

EMB can be stopped at 1 month if confirmed to be INH and RIF susceptible

PZA
Limited safety data in pregnancy
Consider in severe or EPTB

TB DISEASE TREATMENT IN HIV

- Same regimen
- Evaluate for drug-drug interactions
  - Isoniazid typically used
- All pregnant people with HIV should be connected to HIV care and on antiretroviral therapy

Isoniazid	• Safe to use during pregnancy • Monitor for symptoms/signs of liver toxicity • Consider monthly LFTs (esp if known liver disease) • Administer with pyridoxine (B6) supplements
Rifampin	• Safe to use during pregnancy • Consider vitamin K supplements to prevent anemia in newborn
Pyrazinamide	• Unclear if crosses placenta • Use worldwide suggests likely to be safe in pregnancy • Monitor for symptoms/signs of liver toxicity • Consider monthly LFTs (esp if known liver disease) • Individualized use, shared decision making (HIV, severe, EPTB) • Included in WHO recommended treatment regimen • If used may be able to shorten duration to 6 months
Ethambutol	• Safe to use during pregnancy

MONITORING ON TB DISEASE TREATMENT

- Baseline
  - Liver function tests (ALT, AST, bilirubin)
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- During treatment
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DRUG RESISTANT TB

- Limited data – generally good outcomes
- Pregnant people excluded from BPaL and other RR/MDR-TB trials
- Bedaquiline
  - Safe in small cohorts
  - May be associated with lower birth weight infants
  - Monitoring: ECG, fetal growth
- Pretomanid
  - Not used in pregnancy
  - Testicular toxicity in mice studies
- Linezolid
  - Safe in small cohorts
  - Associated with bone marrow suppression, anemia
  - Monitoring: CBC, visual acuity and peripheral neuropathy

BREASTFEEDING

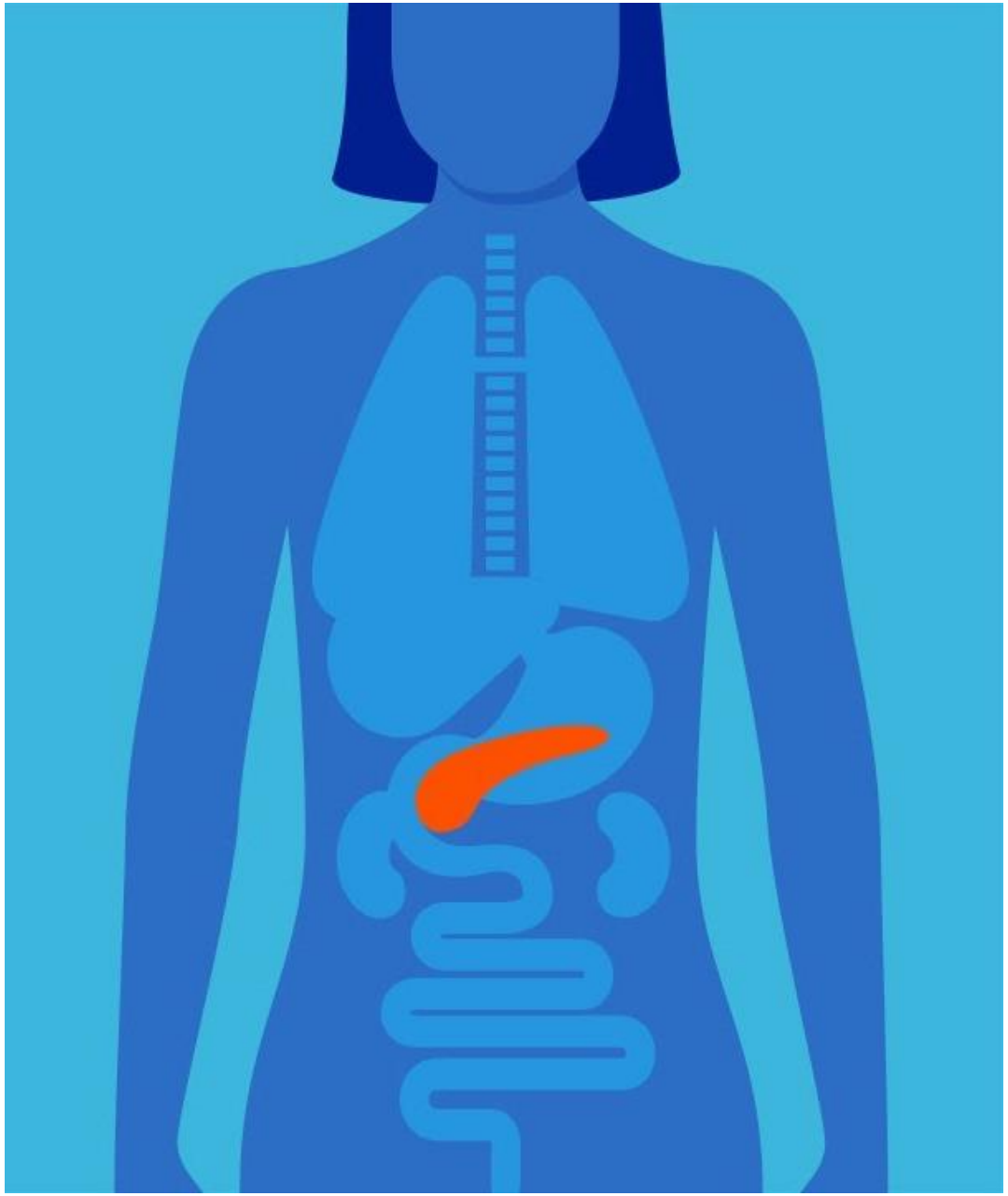
- Encouraged if on first line therapy for at least 2 weeks
- Pyridoxine recommended for all breastfeeding persons on isoniazid
- No known infant toxicity related to TB drugs seen with breastfeeding, limited direct data on drug presence in breastmilk
- Can take TB drugs immediately after feeding and before infant's longest sleep period to minimize exposure
- Breastfeeding is not effective treatment for TB disease or LTBI in infant

Isoniazid	Present in breastmilk, unlikely to exceed recommended infant doses
Rifampin	Low breastmilk concentrations (modeling studies), likely low infant exposure. May cause breastmilk discoloration.
Pyrazinamide	Low measured breastmilk concentrations, unlikely to exceed recommended infant doses
Ethambutol	Low measured breastmilk concentrations, unlikely to exceed recommended infant doses

INFECTION PREVENTION IN TB DISEASE

- Mother should wear a mask until no longer infectious
- No difference in risk of transmission if on effective TB therapy
- Standard infection prevention practices during pregnancy, labor, delivery and postpartum period
- Avoid separating parent and newborn
- Inappropriate infection control practices can increase stigma, lead to adherence issues

DIABETES



38 million people (15%) of US adults have diabetes

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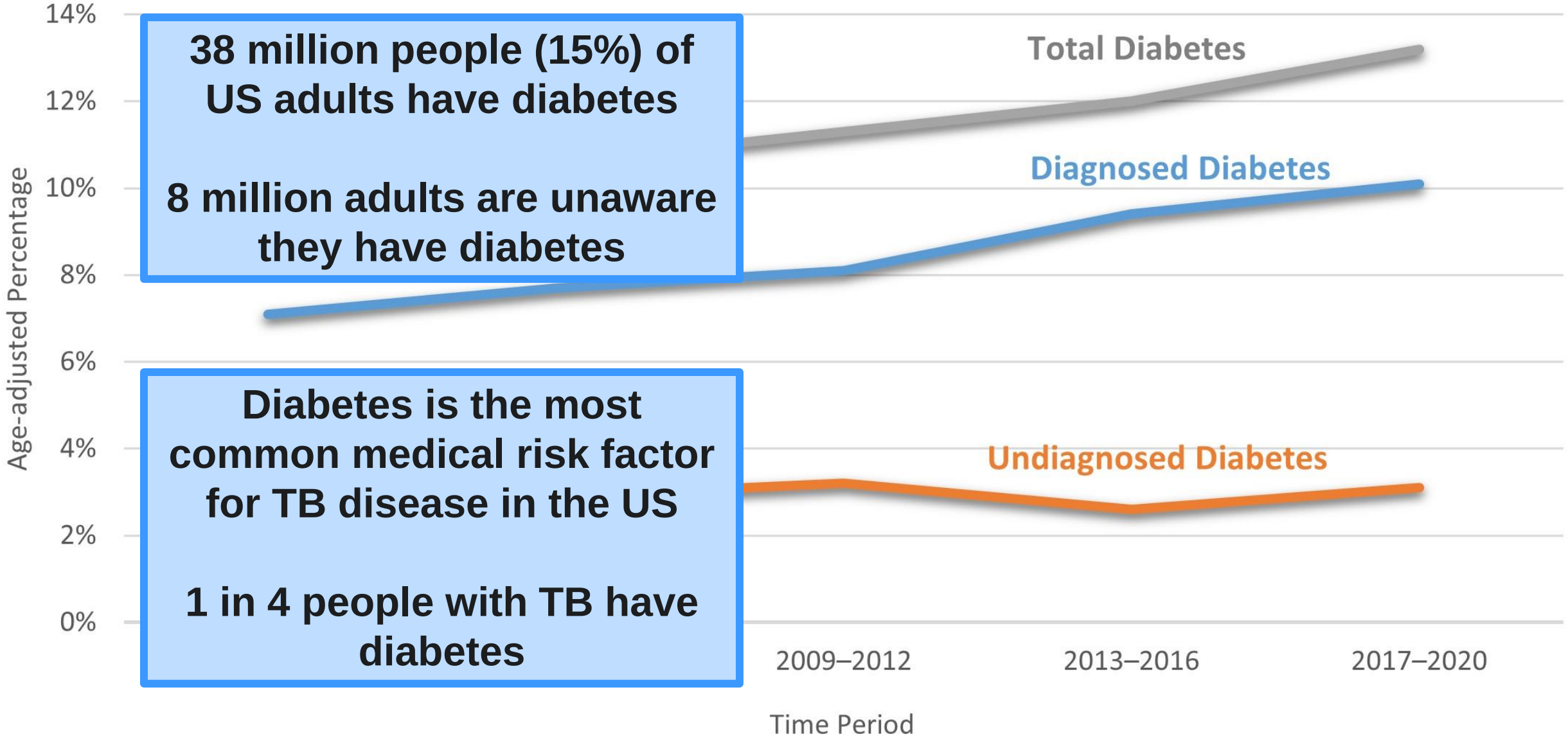
1 in 4 people with TB have diabetes



Type 1 Diabetes Mellitus

- Autoimmune destruction of insulin producing cells in pancreas
- Most diagnosed in childhood
- Rapid onset
- Requires insulin

Type 2 Diabetes Mellitus

- Resistance to insulin or insufficient insulin production
- More gradual onset
- Can use oral and other injectable diabetes treatments

Complications of diabetes

Macrovascular

Cardiovascular disease

Cerebrovascular disease

Peripheral arterial disease

Microvascular

Kidney disease (nephropathy)

Eye disease (retinopathy)

Peripheral nerves (neuropathy)

PRESENTATION OF DIABETES

- Polyuria – need to urinate frequently
- Polydipsia – increased thirst and fluid intake
- Tiredness and fatigue
- Unexpected weight loss

- **Risk factors**
  - Older age
  - Overweight and obesity (central)
  - Family history of DM
  - Ethnicity (American Indian, Black, Hispanic, Asian, Pacific Islander)
  - History of gestational DM, elevated blood glucose

Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

Diabetes Care 2024;47(Supplement_1):S20–S42

DIABETES & TUBERCULOSIS

- Diabetes increases the risk of TB disease
- Even greater increase with DM + other risk factors (HIV, tobacco)
- TB may progress faster, more systemic symptoms, more smear/culture +
- TB severity and outcomes related to glycemic control

Rehman AU et al. Front Public Health. 2023 Nov 16:11:1244450
Khattak M et al. Ann Med. 2024 Dec;56(1):2313683

DIABETES & TUBERCULOSIS

- Increased risk of adverse outcomes
  - Prolonged smear and culture positivity at 2-3 months
  - Increased relapse and recurrence, emergence of resistant TB
  - Treatment prolongation
  - Hepatotoxicity, renal toxicity
  - Mortality
- Potential reasons for worse outcomes
  - Immunosuppressive effects of diabetes
  - Drug interactions
  - Medication adverse effects
  - Adherence
  - Reduced drug bioavailability

Rehman AU et al. Front Public Health. 2023 Nov 16:11:1244450
Khattak M et al. Ann Med. 2024 Dec;56(1):2313683

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POLL OPEN

Which of the following people with TB should be screened for diabetes?

1. 45-year-old man with normal BMI
2. 28-year-old woman with BMI of 42
3. US mainland born, 28-year-old Samoan woman with normal BMI
4. ✓ All of the above

SCREENING FOR DIABETES

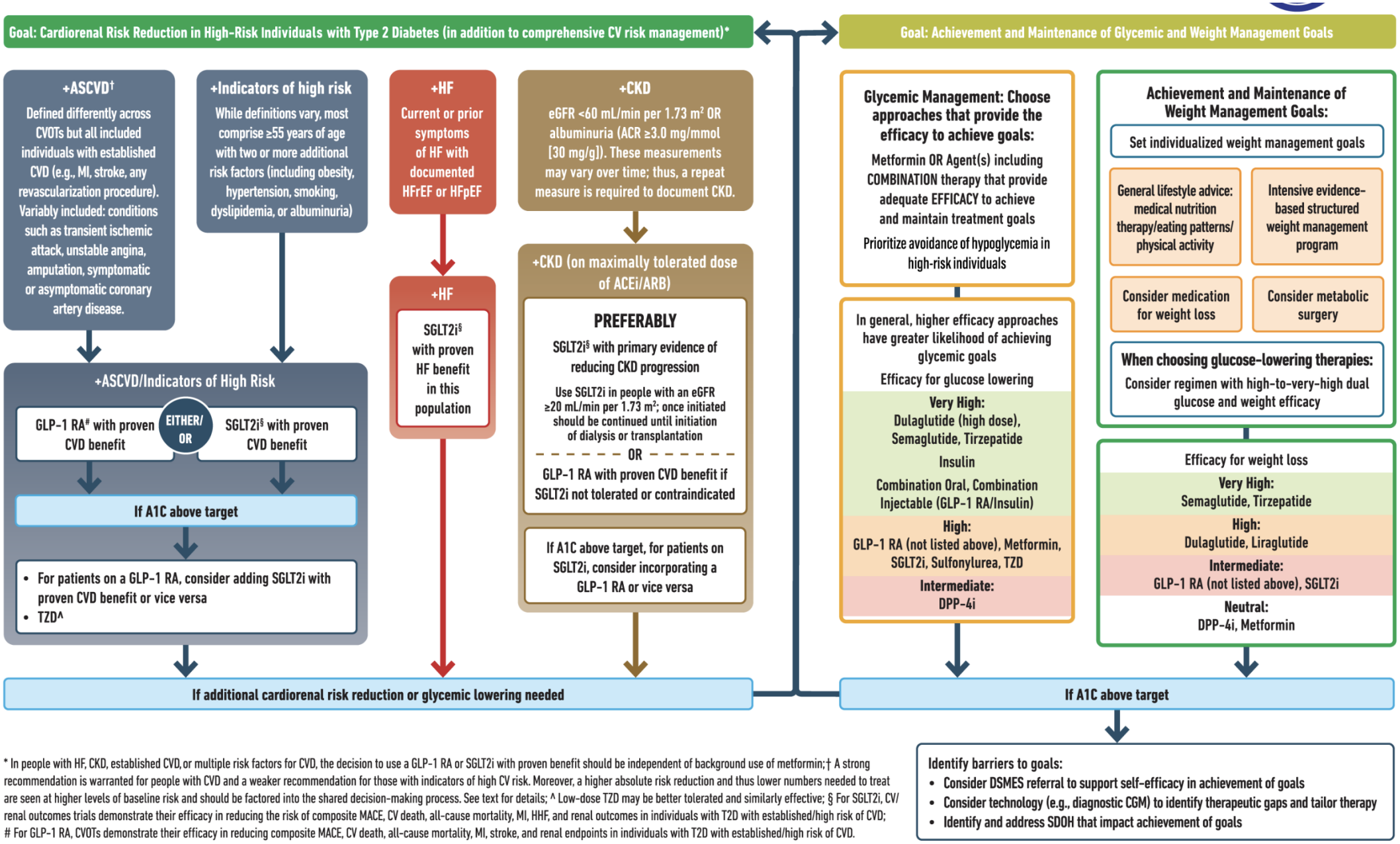
- Ideally screen everyone with TB disease

- Definitely screen if risk factors
  - Age >40
  - BMI >25
  - First degree relative with diabetes
  - Ethnicity (American Indian, Black, Hispanic, Asian, Pacific Islander)
  - Alcohol excess
  - Prior gestational DM or pre DM

DIABETES MANAGEMENT

- **Dietary changes, exercise, weight reduction**
- **Medications**
  - Metformin
  - Sulfonylureas (glipizide, glyburide, glimeprimide)
  - Other oral and injectable agents
  - Insulin
- **Address CVD risk**
  - Consider statins +/- aspirin

Glycemic goals	
Most people	A1C ≤7.0 % Fasting glucose 80 to 130 mg/dL Postprandial glucose <180 mg/dL
Older patients	A1C ≤8.0 % Fasting glucose 80 to 130 mg/dL Postprandial glucose <180 mg/dL
Pregnancy	A1C ≤6.0 %



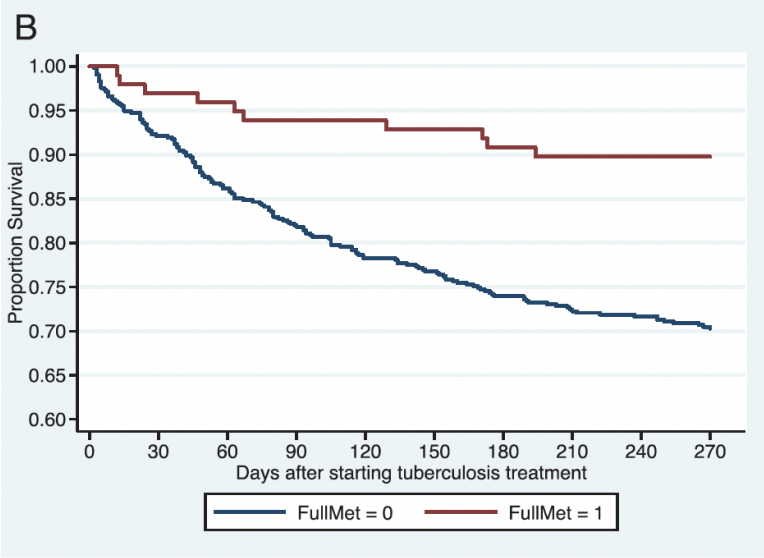
* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

ADA Diabetes Management Guidelines. Diabetes Care 2024;47(Supplement_1):S158–S178

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

Nicholas R. Degner,[1] Jann-Yuan Wang,[2] Jonathan E. Golub,[1,3,4] and Petros C. Karakousis[1,4]

[1]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [2]Department of Internal Medicine, National Taiwan University Hospital, Taipei; and [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, and [4]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland



	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

Metformin use among patients with DM during TB treatment. Patients with documented use of metformin for ≥80% of tuberculosis treatment.

Retrospective cohort study of 2416 adults and adolescents on TB treatment

Diabetes

1.91 x higher odds of death (adjusted)

1.72 x higher odds of remaining culture positive at 2 months

Metformin – decreased mortality

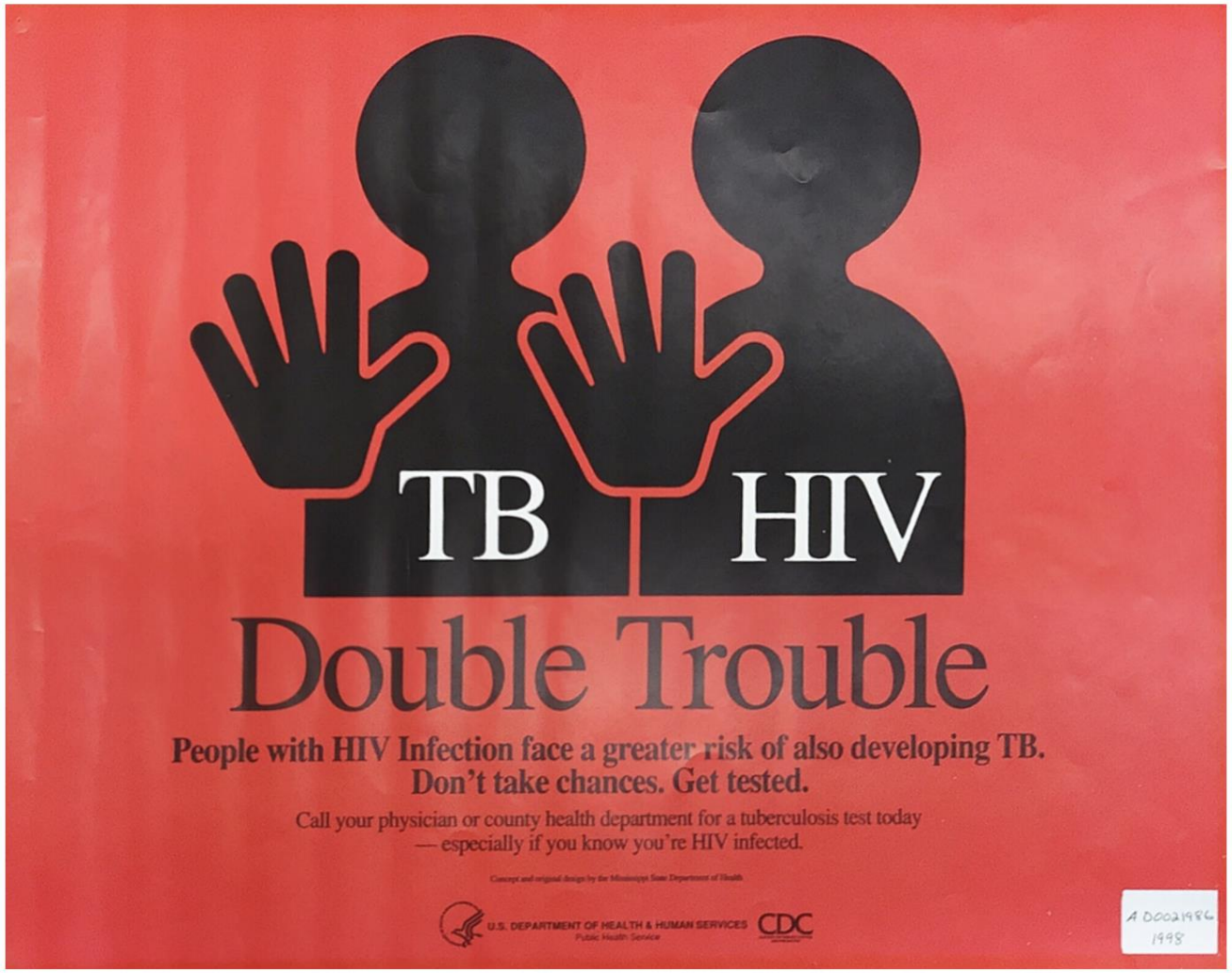
Degner NR et al. Clin Inf Dis 2018;66(2):198–205

DRUG INTERACTIONS

- Potential for interactions between TB drugs (rifampin) and diabetes drugs

- Rifampin
  - Moderate CYP2C9 inducer
    - Decreases sulfonylureas – monitor for efficacy
  - Strong CYP3A4 inducer, P-glycoprotein inducer
    - Decreases linagaliptin (DPP-4 inhibitor) – consider alternative therapy
  - Moderate CYP2C8 inducer
    - Decreases pioglitazone (thiazolidinedione) – monitor for efficacy

HIV



TB AND HIV CO-INFECTION

- HIV infection increases risk of developing TB disease
- Manifestations of TB disease depend on the degree of immunosuppression
- Broader differential diagnosis of symptoms
    - HIV infection
    - Tuberculosis
    - Other opportunistic infections
- Increased risk of extrapulmonary TB
- Everyone with HIV should be connected to HIV care and on antiretrovirals

TB AND HIV INFECTION

Early HIV infection (CD4 ≥ 200 cells/mm^3)

- Similar presentation to HIV uninfected
- Fever, cough, weight loss, anorexia, fatigue, weight loss, night sweats
- Upper lobe, cavitary pulmonary disease

TB AND HIV INFECTION

Advanced HIV infection (CD4 < 200 cells/mm^3)

- More variable pulmonary infiltrates, less typical distribution
- Extrapulmonary TB
- Disseminated TB
- May also be subclinical with no or minimal symptoms, normal CXR

OTHER OPPORTUNISTIC INFECTIONS

- More than one opportunistic infection is possible in immunologically advanced HIV infection
- May require treatment for multiple infections or malignancies
- Increases possibilities of drug adverse effects, toxicities and interactions
- Trimethoprim-sulfamethoxazole prophylaxis (Pneumocystis, Toxoplasma) may also be needed if CD4 count is less than 200

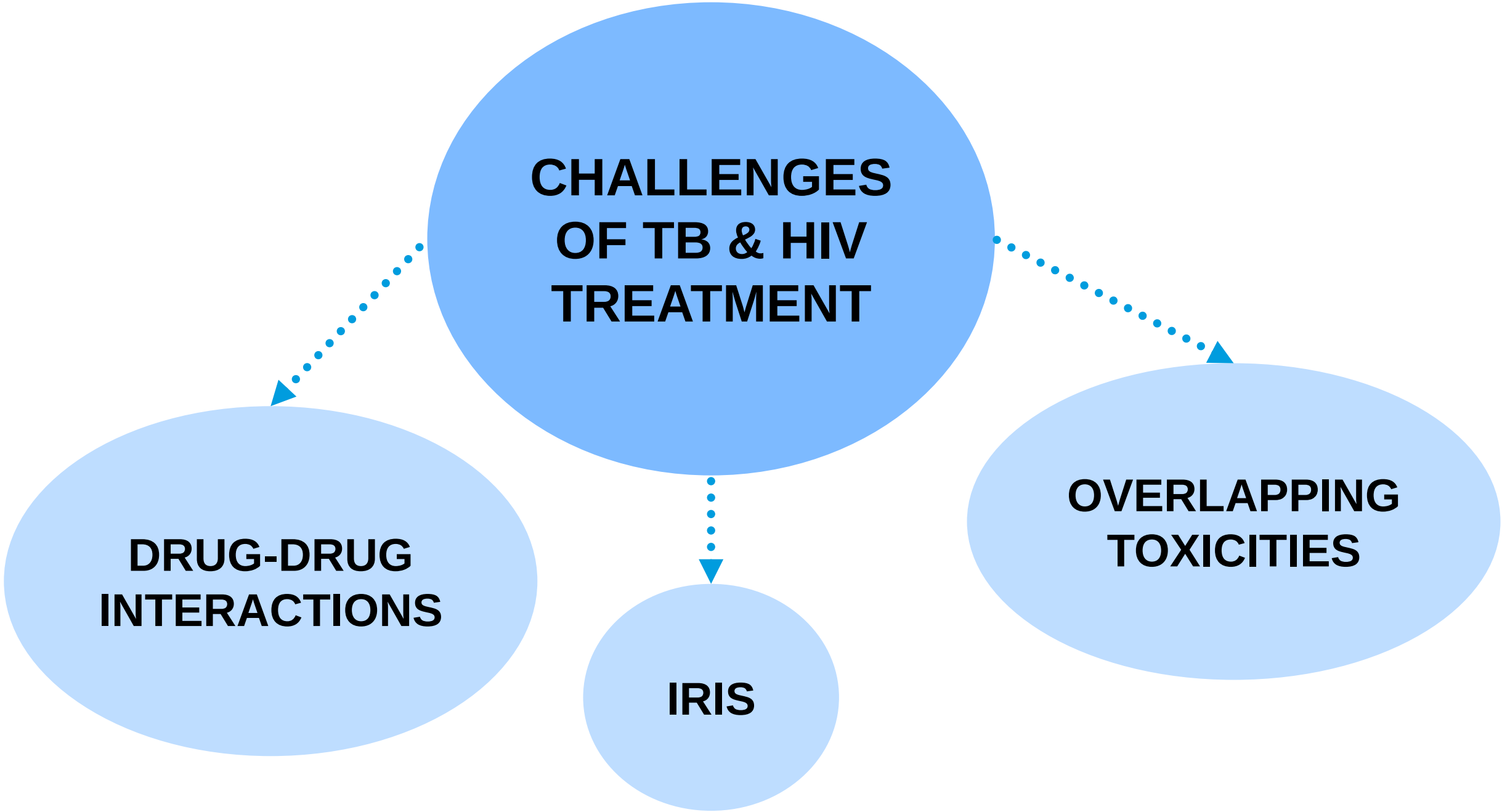
Subclinical tuberculosis among adults with HIV: clinical features and outcomes in a South African cohort

Kristina L. Bajema[1*], Ingrid V. Bassett[2], Sharon M. Coleman[3], Douglas Ross[4], Kenneth A. Freedberg[2], Anna Wald[5] and Paul K. Drain[6,7]

- 654 adults with untreated HIV, median CD4 count 206
- At enrolment: TB symptom screening, single sputum specimen

Active TB N=96 (15%)	**Subclinical TB** N=28 (4%)	**ATT, negative micro** N = 40 (6%)
AFB smear positive 14%	AFB smear positive 29%	
Median CD4 count 68	Median CD4 count 136	Median CD4 count 90
Death, N=25 (26%)	Death, N=3 (11%)	Death, N=5 (13%)

Bajema et al. BMC Infectious Diseases (2019) 19:14



Treatment Complexities Among Patients with Tuberculosis in a High HIV Prevalence Cohort in the United States

Destani J. Bizune,[1] Russell R. Kempker,[2] Michelle Kagei,[3] Aliya Yamin,[4] Omar Mohamed,[4] David P. Holland,[2,4] Alawode Oladele,[5] Yun F. Wang,[6,7] Paulina A. Rebolledo,[1,2] Henry M. Blumberg,[1,2] Susan M. Ray,[2] and Marcos C. Schechter[2]

- Retrospective cohort of 274 adults with culture confirmed TB, 2008-2015, Atlanta GA
- 96 (35%) patients with HIV, median CD4 count of 86, 81% on ART during TB treatment

	TB N=178 (65%)	**HIV-TB** N=96 (35%)
Treatment interruption due to AEs	15%	34%
Hospital readmission	21%	50%
Median TB treatment	8.8 months	9.9 months
Cure	85%	75%

Bizune DJ et al. AIDS Res Hum Retroviruses 2018 Dec 1; 34(12): 1050–1057

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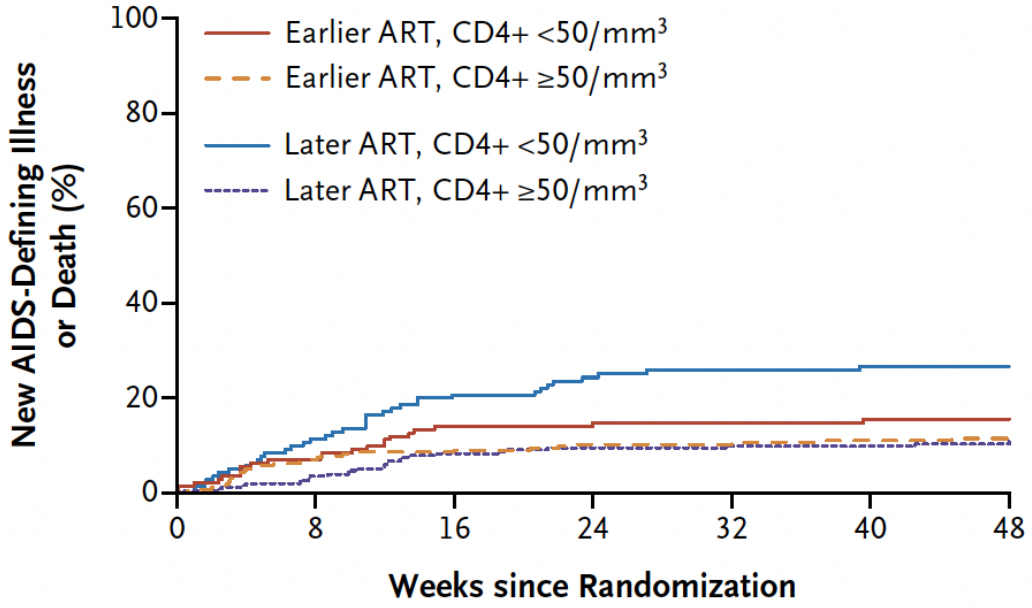
POLL OPEN

When should HIV antiretroviral therapy be started in people with TB and HIV coinfection?

1. ✓ HIV ART should be started within 2 weeks of TB therapy
2. HIV ART should be started within 2 months of TB therapy
3. HIV ART should be started within 4 months of TB therapy
4. HIV ART should be started after completion of TB therapy

WHEN TO START ANTIRETROVIRAL THERAPY

- Early ART is associated with significant benefits
  - Reduced mortality in those with CD4 count < 50 cells/mm^3
  - Reduced AIDS defining events
- Benefits of early ART are not outweighed by potential complications
  - Increased risk of IRIS
  - No difference in treatment limiting drug toxicities



No. at Risk

Earlier therapy							
CD4+ <50/mm^3	144	132	121	121	118	114	74
CD4+ ≥50/mm^3	261	236	225	220	217	210	152
Later therapy							
CD4+ <50/mm^3	141	125	110	103	101	98	69
CD4+ ≥50/mm^3	260	246	232	226	224	220	149

Havlir DV et al. N Engl J Med 2011;365:1482-91

Burke RM et al. J Int AIDS Soc 2021 Jul; 24(7): e25772

WHEN TO START ART

- **Start ART as soon as possible for anyone with TB coinfection***
  - CD4 count < 50 cells/mm^3: Start ART as soon as possible, within 2 weeks of starting TB treatment
  - CD4 count ≥ 50 cells/mm^3: Start ART within 8 weeks of starting TB treatment (ideally still within 2 weeks)

Exception: TB meningitis

ART should not be initiated in the first 8 weeks of TB treatment

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. 2023

WHAT ANTIRETROVIRAL THERAPY TO START

- With rifampin
  - Efavirenz 600 mg once daily
  - Dolutegravir 50 mg twice daily

- With rifabutin
  - Efavirenz 400 mg once daily, rifabutin 450-600 mg daily
  - Dolutegravir 50 mg once daily

RIFAMYCIN DRUG-DRUG INTERACTIONS

- Induce metabolizing enzymes and efflux transporters
  - Metabolizing enzymes
    - CYP3A4 substrates: Protease inhibitors, rilpivirine, rifabutin
    - CYP2B6 substrates: Efavirenz
    - UGT1A1: InSTIs
  - Efflux transporters
    - P-glycoprotein: Protease inhibitors, tenofovir alafenamide

- Rifamycin enzyme induction is maximal at 2 weeks after starting and persists for up to 4 weeks after stopping rifamycin
- Potency of induction: Rifampin, rifapentine > rifabutin

	PROTEASE INHIBITORS	InSTIs	NNRTIs	NRTIs
RIFABUTIN	• Rifabutin 150 mg daily • Only with ritonavir boosting, not cobicistat	• No DTG dose change, rifabutin 300 mg daily • No RAL dose change • BIC, CAB IM, EVG/c not recommended	• Increase DOR to 100 mg bid • EFV 450-600 mg/day • Increase RPV 50 mg daily	• TAF not recommended • No TDF dose change
RIFAMPIN	Coadministration not recommended	• DTG 50 mg bid • RAL 800 mg bid • BIC, CAB IM + PO, EVG/c not recommended	• EFV 600 mg daily • Other NNRTIs not recommended	• TAF not recommended • No TDF dose change
RIFAPENTINE	Coadministration not recommended	• Can use with DTG 50 mg daily, RAL 400 mg bid • BIC, CAB IM + PO, EVG/c not recommended	• No EFV dose change • Other NNRTIs not recommended	• TAF not recommended • No TDF dose change

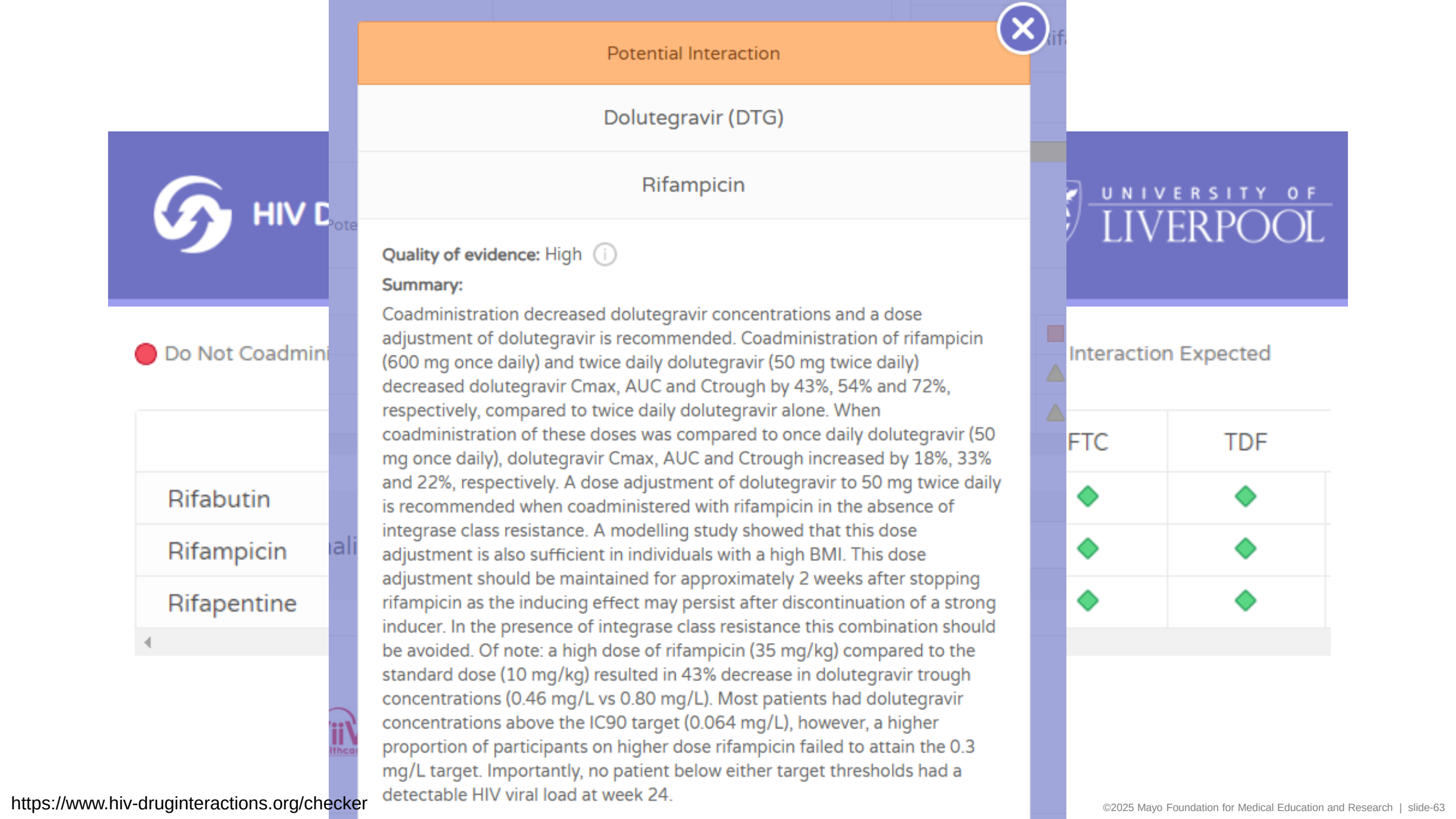
HIV Drug Interactions

UNIVERSITY OF LIVERPOOL

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected

	DTG	EFV	FTC	TDF
Rifabutin	◆	■	◆	◆
Rifampicin	■	▲	◆	◆
Rifapentine	■	▲	◆	◆

https://www.hiv-druginteractions.org/checker



https://www.hiv-druginteractions.org/checker

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

- Advanced HIV being treated for TB are at significant risk of immune-mediated deterioration during the first weeks of starting or restarting ART, or switching to an effective regimen
- Rapid decrease in HIV viral load and early immune recovery on ART leads to an enhanced immune response to TB bacteria
- TB-IRIS occurs in around 18% after initiation of ART

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

- Manifestations
  - Inflammation at site of TB disease with recurrent local symptoms
  - Systemic inflammation symptoms (fevers, sweats, weight loss etc)
  - Enlarged, suppurative lymphadenopathy
  - Abscess formation
  - Worsening infiltrates, effusions or other radiologic findings
  - Granulomatous hepatitis

- Median onset: 14 days after starting ART
- Can be delayed upto 3 months

DIAGNOSIS OF TB-IRIS

- Typical clinical features
  - Initial reliable TB diagnosis
  - Initial response to TB treatment
  - Deterioration with compatible symptoms, signs and imaging within 3 months of starting ART

- Exclusion of alternative diagnoses (eg. TB drug resistance)

RISK OF IRIS

- Lower CD4 count (<50 cells/mm3)
- High HIV viral load
- Short interval between starting ATT and ART
- Extrapulmonary or disseminated TB (higher mycobacterial burden)

MANAGEMENT OF TB-IRIS

- Low mortality 1-2% (except TB meningitis)
- Significant morbidity

- Treatment:
  - Continue ART and TB therapy
  - Evaluate for treatment failure, other infections or diseases
  - Prednisone course
    - If no evidence of treatment failure or other opportunistic infection
    - Reduce TB IRIS morbidity

PREDNISONE PROPHYLAXIS

- Randomized, double-blind, placebo-controlled trial of 240 people initiating HIV ART, had started TB treatment within 30 days before ART
- Prednisone 40 mg daily for 14 days, then 20 mg per day for 14 days
- Median CD4 49
- TB IRIS: 32% in prednisone vs 46% in placebo
- Deaths: 5 in prednisone vs 4 in placebo
- Severe infections: 11 in prednisone vs 18 in placebo
- Consider pre-emptive prednisone in high risk (starting ART within 30 days of starting ATT, CD4 ≤100/mm3) who are responding well to ATT and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B

Meintjes G et al. N Engl J Med 2018; 379:1915-1925

QUESTIONS & DISCUSSION