61ST ANNUAL

Denver TB Course

(Hybrid Event)

APRIL 2-4, 2025

National Jewish Health®

Updates in the management of TB infection and disease in people living with HIV

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- National Jewish Health

Disclosures

- I have nothing to disclose

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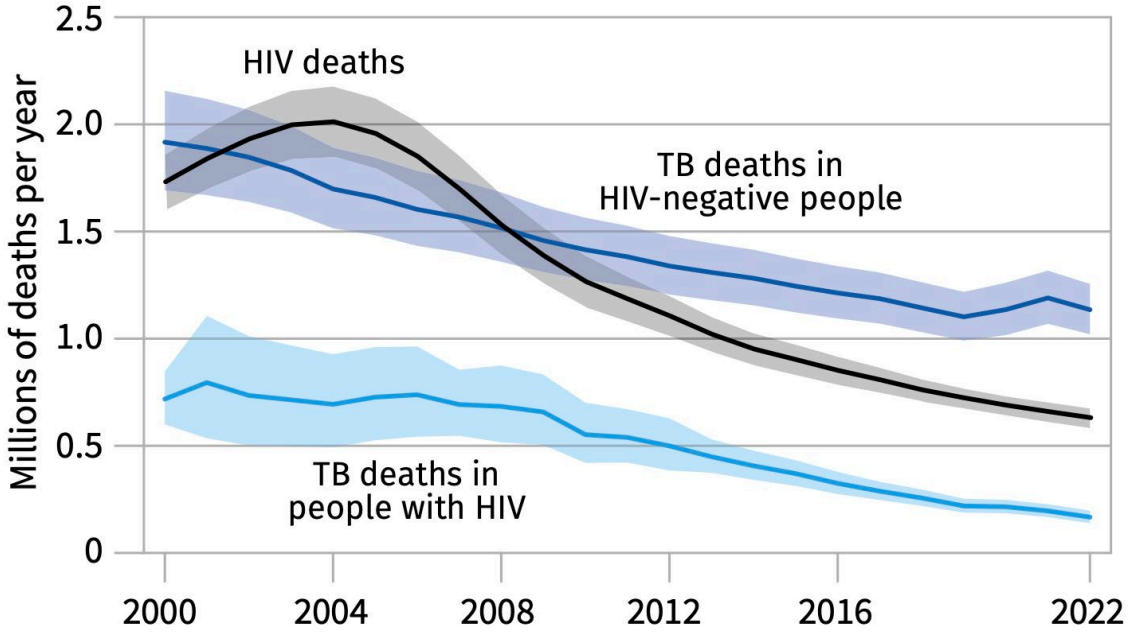
Objectives

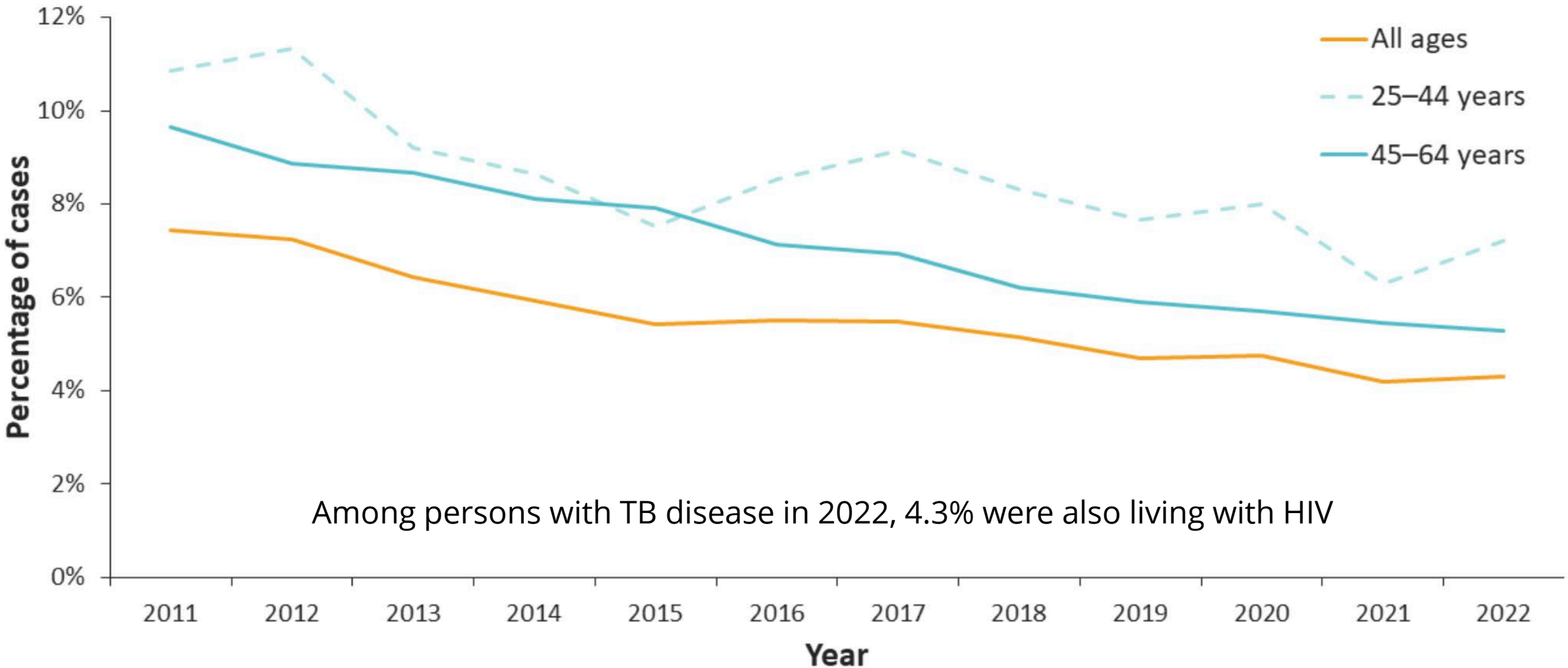
- Gain an understanding of diagnostic tools for Tuberculosis-HIV (TB-HIV)
- Be able to discuss specific treatment considerations for TB disease in people living with HIV (PLHIV)
- Be able to discuss LTBI treatment options for PLHIV on ART



- In 2023, TB caused an estimated 1.3 million (range 1.18-1.43) deaths among HIV-negative people
  - additional 167,000 deaths from TB (range, 139 000–198 000)) among people with HIV
- 10.6 million people (range, 9.9–11.4 million) developed TB disease in 2023:
  - 1.3 million children

Global TB Report 2023

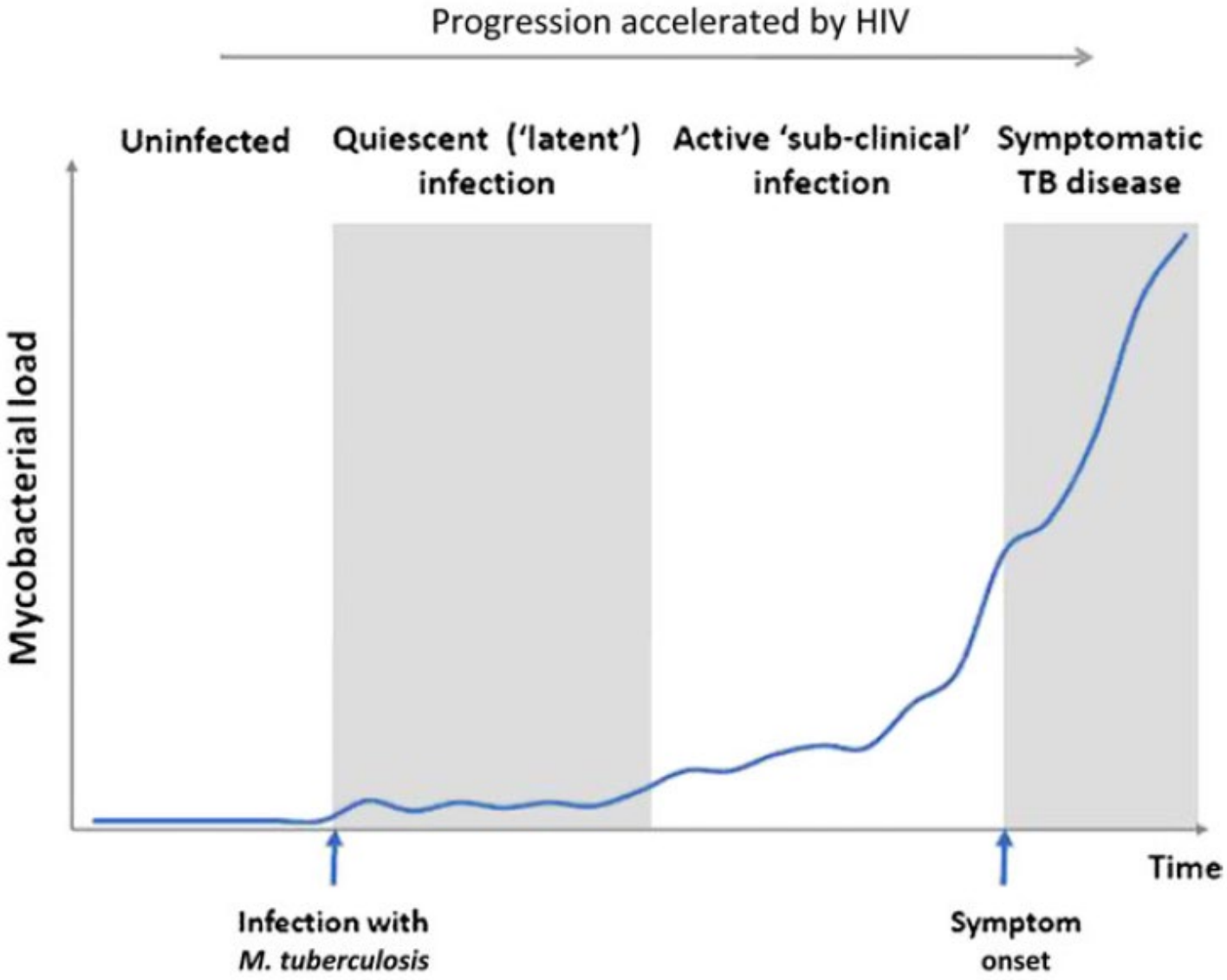
Percentage of HIV Coinfection by Age Among Persons with TB,* United States, 2011–2022



Among persons with TB disease in 2022, 4.3% were also living with HIV

*Persons alive at diagnosis with HIV test results

The Spectrum of TB Infection in people living with HIV-TB



Lawn, SD and Wood R, JID 2011

ART coverage in people with HIV and TB in 2022—gaps in care remain

- 85% of people with HIV who were newly diagnosed with TB were on ART
- Estimates of all individuals with HIV who had TB indicate ART coverage is closer to 54%
  - By contrast all people with HIV who were also on ART is estimated at 76%
    - Gap between estimated # with HIV who developed TB and *those who were actually diagnosed with TB*
      - Gap is estimated at 244,042 individuals

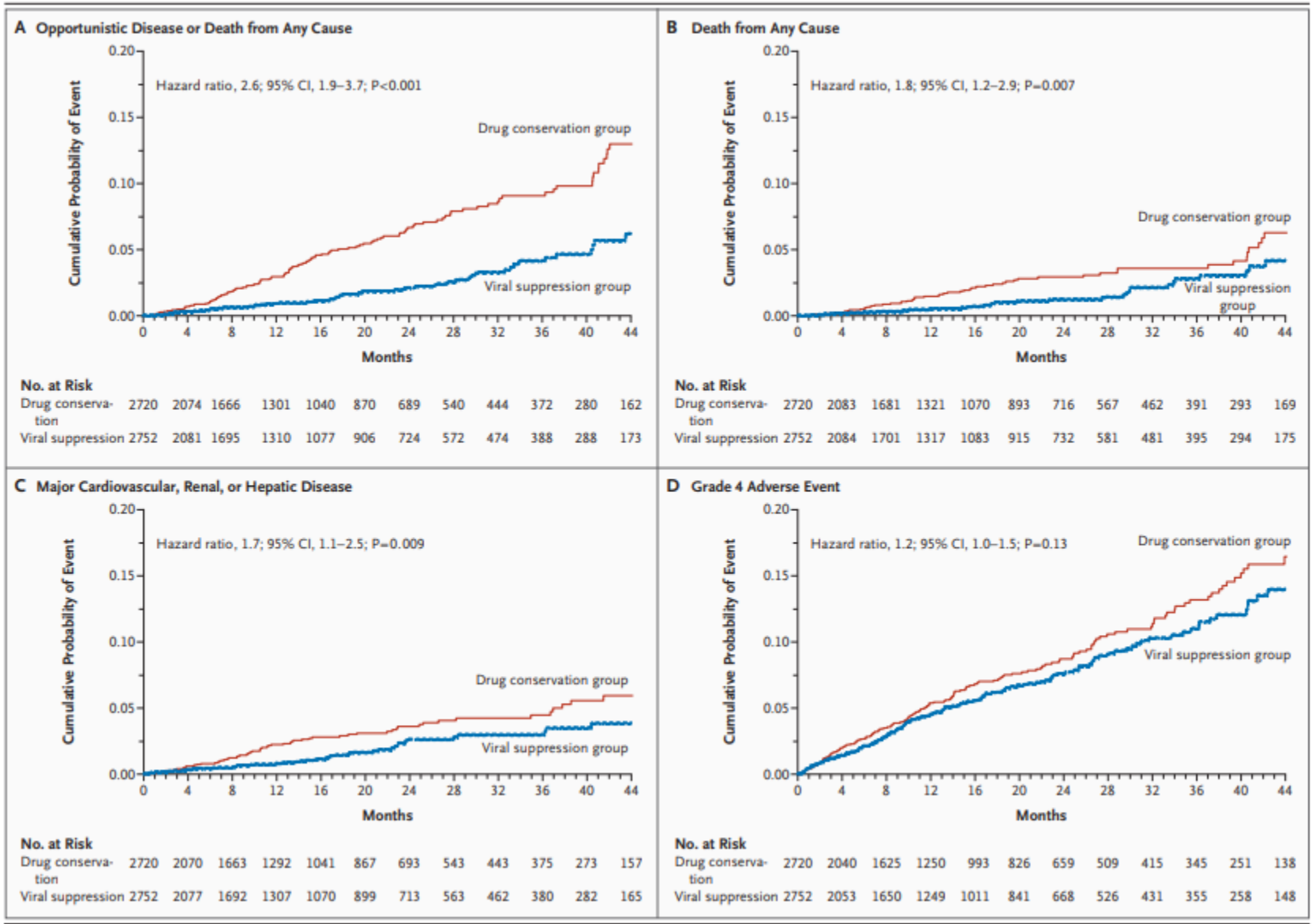
Even short ART treatment interruptions increase risk of death

ESTABLISHED IN 1812 NOVEMBER 30, 2006 VOL. 355 NO. 22

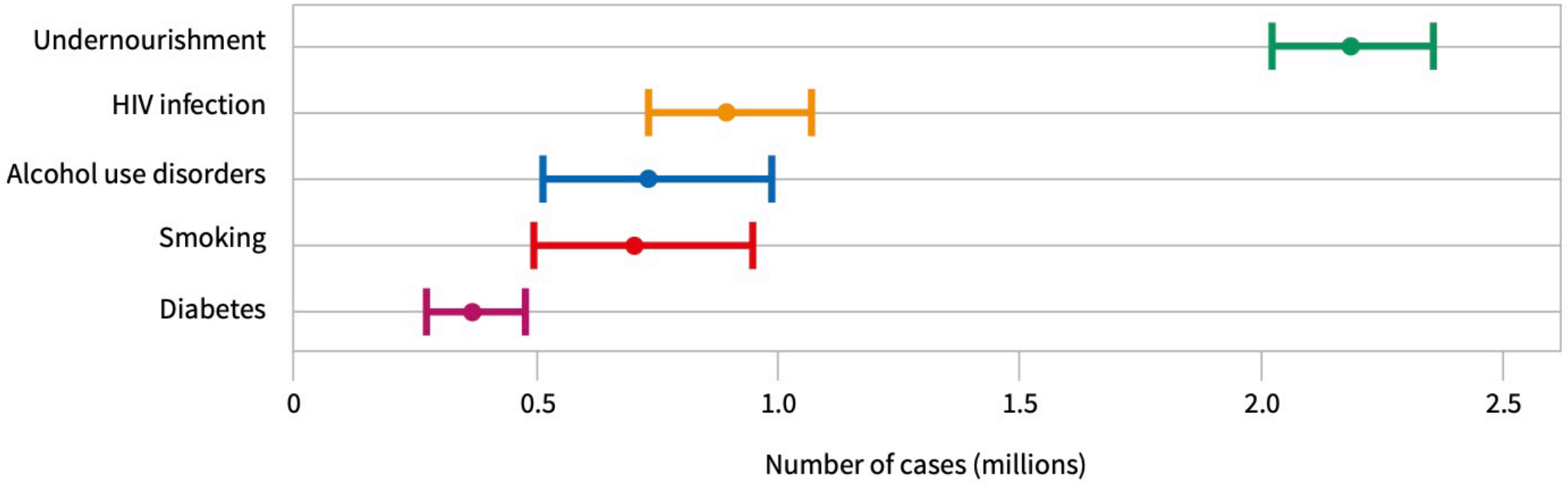
CD4+ Count–Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group*

- average CD4+ count decreased by 87 cells per cubic millimeter per month during the first 2 months after randomization among participants in the drug conservation group
- increase in the percentage of patients with a detectable plasma HIV RNA level from 6% to 72%) within 2 months after the cessation of antiretroviral therapy in the drug conservation group
- Increased risk of death, cardiovascular disease and opportunistic infections
  - Seen as early as 4-8 months after interruptions



Global estimates of the number of TB cases attributable to selected risk factors,[a] 2022



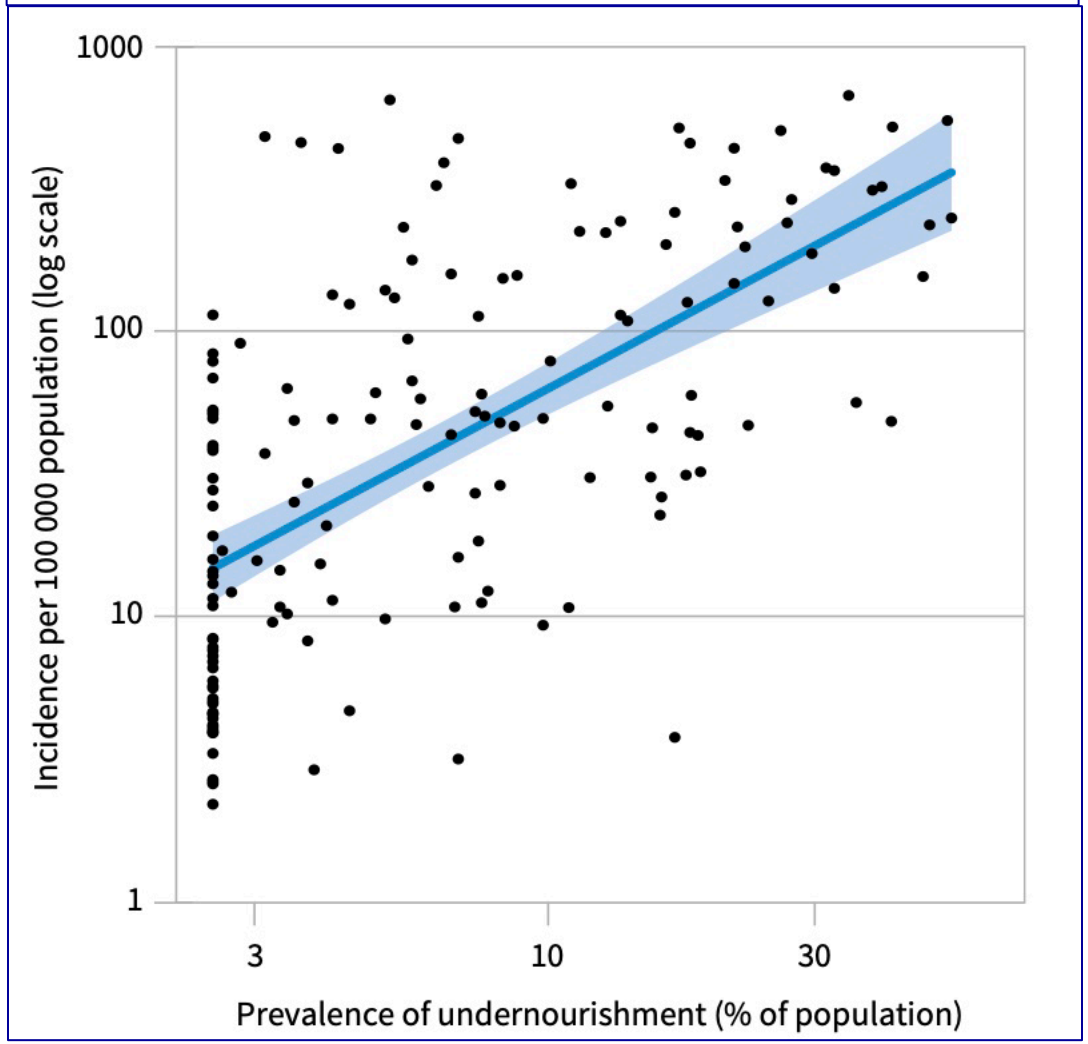
[a] Sources of data used to produce estimates were: Imtiaz s et al. Eur Resp Jour (2017) (https://pubmed.ncbi.nlm.nih.gov/28705945/); Hayashi S et al. Trop Med Int Health (2018) (https://pubmed.ncbi.nlm.nih.gov/30062731/); Lönnroth K et al. Lancet (2010) (https://pubmed.ncbi.nlm.nih.gov/20488524/); World bank sustainable Development Goals Database (http://datatopics.worldbank.org/sdgs/); WHO Global Health Observatory (https://www.who.int/data/gho); and the WHO Global Tuberculosis Programme.

In the US—1 in 4 patients with active TB is also living with diabetes

Competing risk factors and need to treat the "whole patient"

- What interfered with your ability to take your HIV medications?
  - Partner passed away
  - Lost my job
  - House burned down
  - Need to support children's nutritional needs
  - My HIV medications make me hungry

Incidence of TB vs. prevalence of undernourishment



Provision of TB treatment among people living with HIV and TB: combination of TB treatment and ART averted 6.4 million deaths

Cumulative number of deaths averted by a) TB treatment as well as b) antiretroviral treatment for people diagnosed with TB who were also living with HIV, 2010–2022 (in millions), globally and by WHO region

WHO REGION	PEOPLE WITHOUT HIV		PEOPLE WITH HIV[a]		TOTAL	
	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL
African Region	5.2	4.3–6.2	4.8	4.1–5.5	10	8.9–11
Region of the Americas	1.2	1.0–1.3	0.23	0.21–0.24	1.4	1.3–1.5
South-East Asia Region	18	15–21	0.85	0.53–1.2	19	16–22
European Region	1.1	0.95–1.2	0.21	0.18–0.25	1.3	1.2–1.4
Eastern Mediterranean Region	3.4	2.9–3.9	0.062	0.047–0.078	3.5	3.0–4.0
Western Pacific Region	9.0	8.0–10	0.32	0.26–0.37	9.3	8.3–10
Global	**38**	**33–43**	**6.4**	**5.5–7.3**	**44**	**39–49**

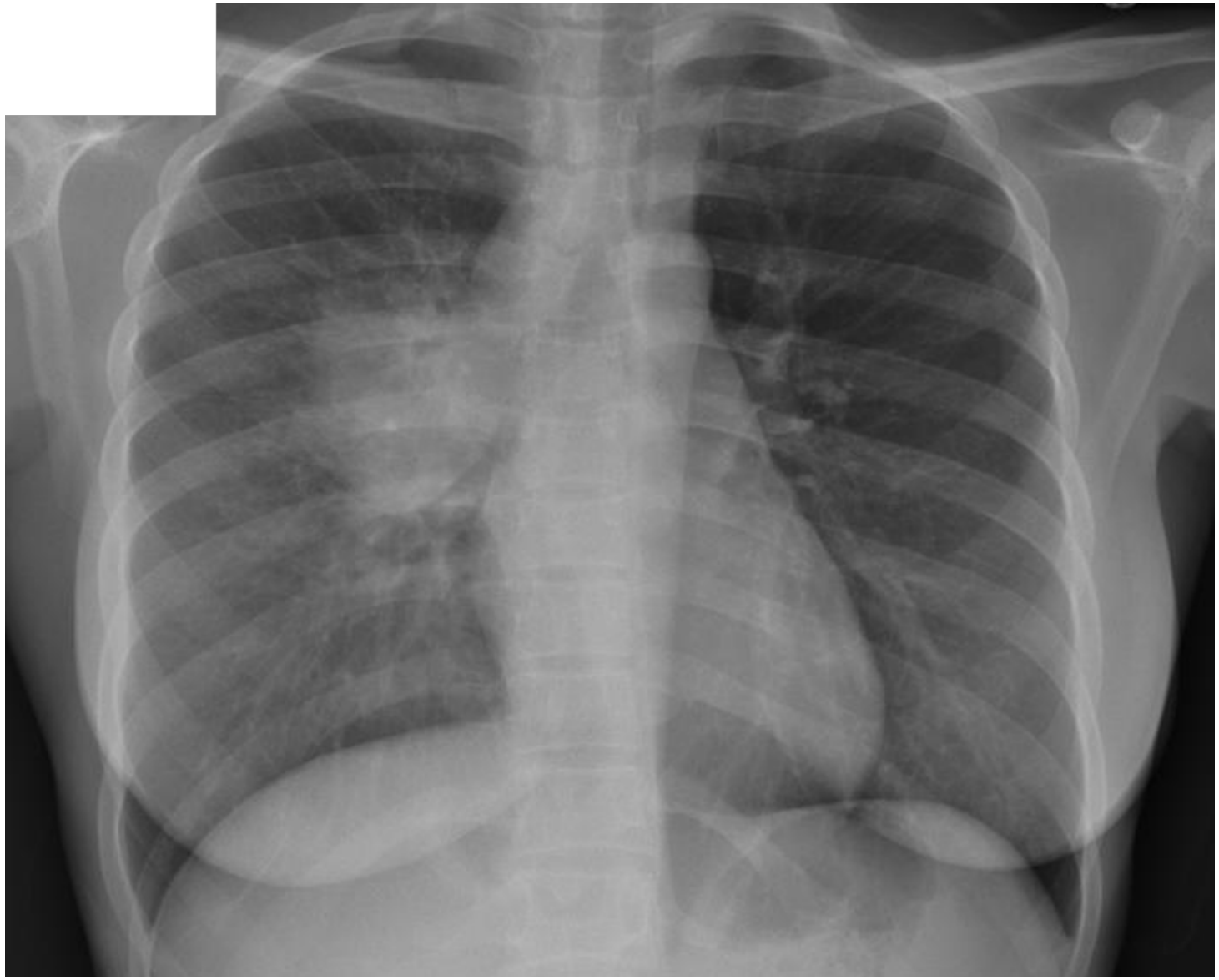
[a] Deaths from TB among people with HIV are officially classified as deaths caused by HIV/AIDS (with TB as a contributory cause). This is the reason why the estimates make a clear distinction between people with and without HIV.

Global TB Report, 2023

HPI

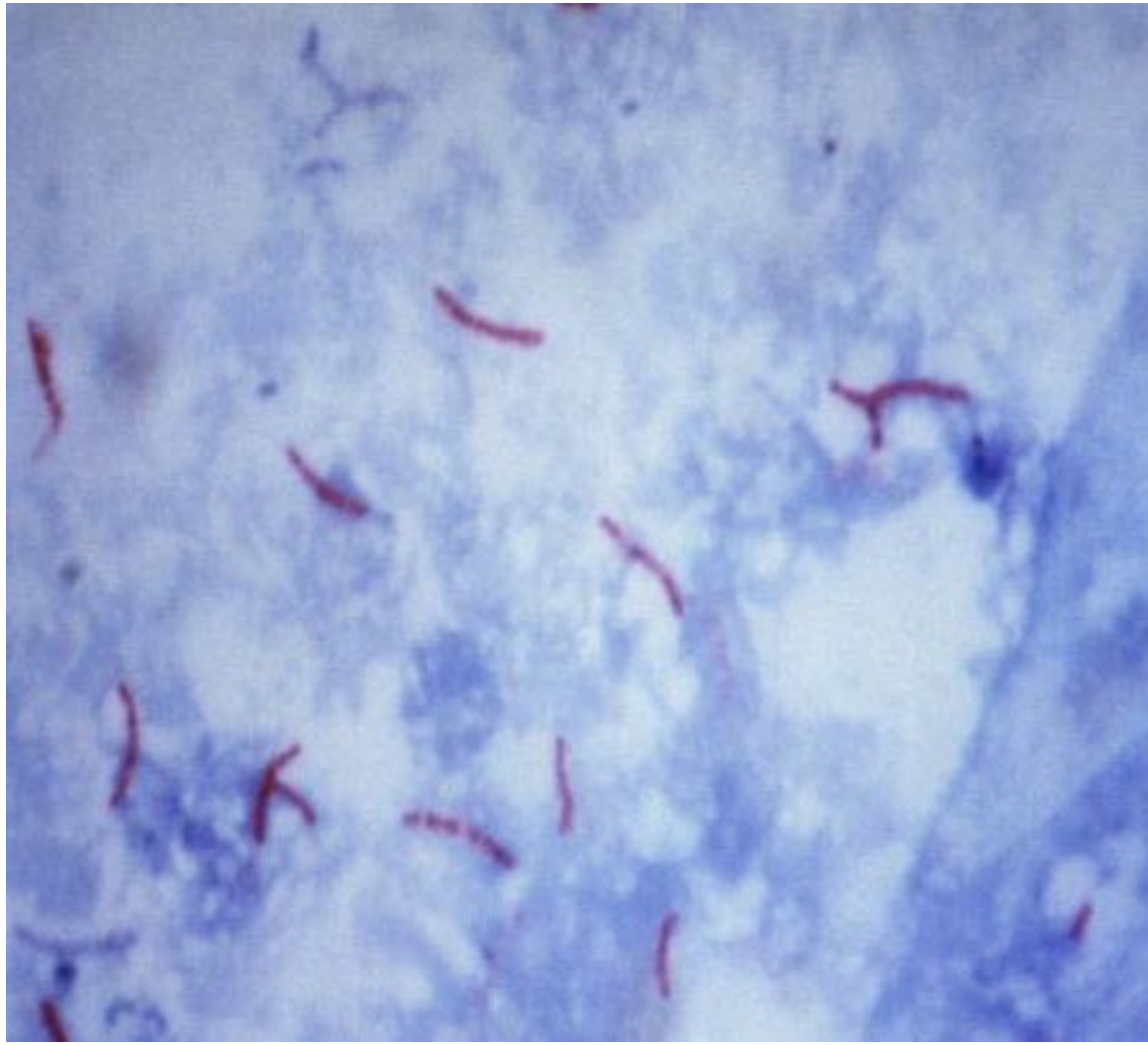
20 y/o woman with newly diagnosed HIV with cough, and lymphadenopathy.

- 15 weeks pregnant
  - Experiencing homelessness



Diagnostic testing for *M. tuberculosis* Disease in PLHIV

- CXR—insensitive, may have normal findings
- (AFB) sputum smear
  - Up to 70% may be smear negative
- PCR based testing: more sensitive than smear
  - May be lower (80% vs. 89% sensitive in HIV vs. no HIV)
- AFB sputum culture—limit of detection 10 organisms/mL sputum



Conde MB. Am J Respir Crit Care Med. 2000;162(6):2238

Bakari M, et al., BMC Infect Dis. 2008;8:32

Hassim S, et al., Clin Infect Dis. 2010;50(7):1053

Steingart KR, et al., Lancet Infect Dis, 2006. 6: 664-74

Steingart KR, et al. *Cochrane Database Syst Rev*. 2014;1:CD009593

GeneXpert for Pulmonary TB

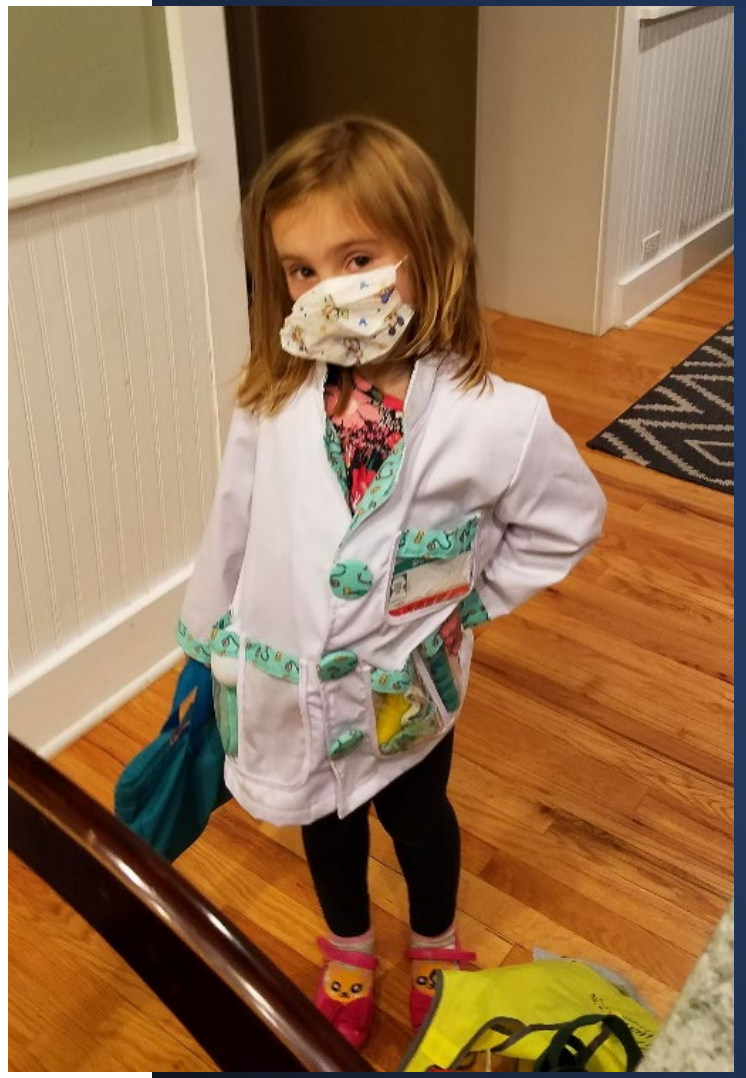
Leutkemeyer CID 2016: 62 (1 May)

Evaluation of Xpert MTB/RIF Versus AFB Smear and Culture to Identify Pulmonary Tuberculosis in Patients With Suspected Tuberculosis From Low and Higher Prevalence Settings

Xpert MTB/Rif for Culture confirmed TB in the US			
Smear	**AFB (+)**	**1 Xpert**	**2 Xpert**
2 AFB Smears (n = 91)			
AFB (+)	68.1%	96.7%	100%
AFB (-)		59.3%	71.4%
3 AFB Smears (n = 53)			
AFB (+)	60.4%	96.8%	100%
AFB (-)		57.9%	70%

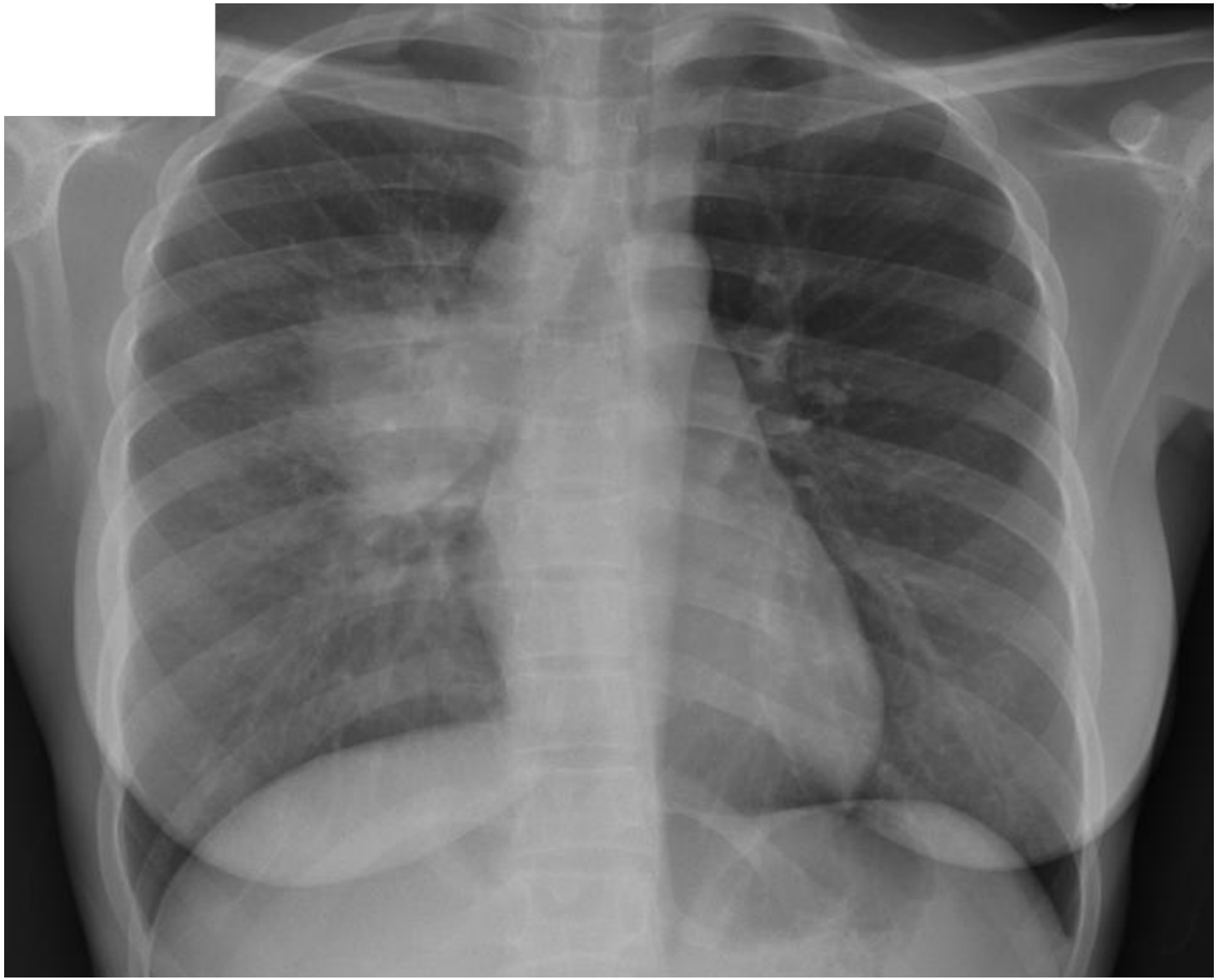
TB diagnostics: summary

- The best test is still culture: unacceptable diagnostic delays
- Point of care testing is improving but there are still gaps…
- What to do?
  - Maintain high index of suspicion
  - Empiric treatment followed by assessing clinical response
    - Pending culture results where available (may not be feasible if practicing in a resource limited setting)



HPI - continued

- Sputum – smear negative X 3
- Gene Xpert MTB/RIF negative
- IGRA positive
- CD4 count 500 cells/µL
- Lived in Kampala for most of her life prior to moving to the US



HPI

- Excisional cervical lymph node biopsy performed
  - Caseating granulomas throughout
  - Rare AFB
- Started on isoniazid, rifampin, ethambutol, pyrazinamide two weeks after initial presentation
- Sputum cultures grew *M. tuberculosis* after 13 days

HPI continued

- She returns to clinic in 2 weeks feeling well.
  - When should we offer antiretroviral therapy?
  - What options are available for antiretroviral therapy?
  - What is the role for trimethoprim-sulfamethoxaxole (TMP-SMX or co-trimoxazole) and when should this be offered?

Summary of the Evidence: IDSA/ATS TB treatment Guidelines

- Standard 6-month regimens for most with drug-susceptible pulmonary TB
- Extend therapy to 9 months:
  - positive cultures at 2 months and cavitary disease
  - ART is not administered or CD4 <100
  - WHO guidelines: no recommendations to extend treatment for drug-susceptible pulmonary TB

Nahid P, et al. Clin Infect Dis 2016; 63 (7): e147-e195.

4-month daily rifapentine-moxifloxacin regimen was non-inferior to standard 4-drug therapy for treatment of drug-susceptible TB in people with HIV

- International randomized open-label phase 3 noninferiority trial of the following:
  - 4-month daily regimen substituting rifapentine for rifampin and moxifloxacin
    - Isoniazid (H), moxifloxacin (M), pyrazinamide (Z), rifapentine (P) x 8 weeks followed by 9 weeks of HMP
    - H, E, Z, P x 8 weeks followed by 9 weeks of HP
    - Standard 6-month regimen.
  - N=194/2516 (7.8%), Median age 35
  - median CD4+ count was 344 cells/µL (interquartile range: 223–455)
  - All on efavirenz-based ART, starting within 8 weeks.
  - Noninferiority criteria were met if the upper bound of the 95% CI of the difference was <6.6% in both the microbiologically eligible and assessable analysis populations
  - Fewer AEs in rifapentine-based regimens (15%) than the control regimen (21%).

- Pettit A, et al. 2023;76(3):e580–e9

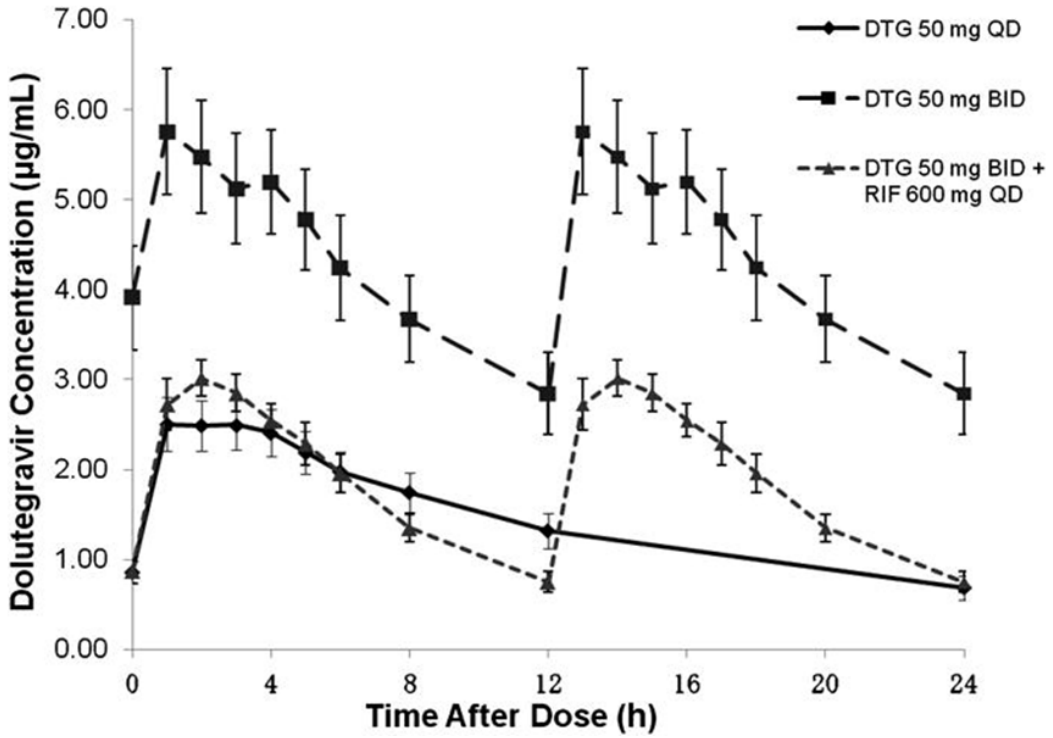
Co-treatment considerations

Trimethoprim-sulfamethoxazole therapy for Patients with TB and HIV

- US guidelines: CD4 count is less than 200 cells/µL, stop when the CD4 count >200 for 3 months
- WHO guidelines: initiate irrespective of CD4 count, continue while on TB treatment
  - Discontinue after TB treatment if:
    - clinically stable on ART, with evidence of immune recovery and viral suppression
  - However, continue if malaria and severe bacterial infections are highly prevalent, irrespective of CD4 count

Effect of rifampin on serum concentrations of dolutegravir (DTG) 50mg BID

- INSPIRING Phase 3b non-comparative open label RCT HIV-TB:
  - DTG 50mg BID + 2NRTIs during TB tx and 2 weeks post therapy vs. Efavirenz (EFV) + 2NRTIs
  - Week 24 of 52:
    - 69 received DTG, 44 EFV
    - Proportions with VL <50 c/mL:
      - DTG 56/69 (81%)
        - 5 discontinued due to protocol deviations/LTFU
      - EVF 39/44 (89%)
        - 2 discontinued due to adverse events



Dooley K et al. CID, 2020

Rifampin Effect on Tenofovir Alafenamide (TAF) Plasma/Intracellular Pharmacokinetics

Healthy volunteers between the ages of 18-65, n=17

- TAF/FTC once daily x 28 days with food, → TAF/FTC once daily with rifampin 600mg daily for 28 days →TDF 300mg daily x 38 days

Intensive PK sampling day 28, day 56 (TAF/FTC+ rifampin) and 84

- Measured TAF, TFV, FTC and (intracellular) IC TFV diphosphate

Plasma TAF Cmax and AUC decreased by 45% and 47% respectively

IC TFV-DP decreased by 40% *but still 82% higher than those achieved by standard dose of TDF*

Case series of 6 individuals presented at ID week, 2022 was reassuring for maintaining viral load suppression

Mohzari Y, et al. Abstract # 1281, ID Week 2022
Cerrone, M et al. JAC 2019

- Healthy volunteers without HIV
  - BID bictegravir with rifampin
  - Levels dropped by 80%
- However, phase 2B study of BID bictegravir, emtricitabine and TAF with rifampin-based TB regimens is currently enrolling in PWHIV-TB
  - Control arm is bid dolutegravir with lamivudine, tenofovir

Custodio J, Abstract # 34, CROI 2018
NCT04734652

Summary of drug-drug interactions with rifampin and rifabutin

TB Drug	ARV Drugs	Daily Dose
Rifampin[a,b] **Note:** DTG, RAL, and MVC doses need to be adjusted when used with rifampin.	HIV PIs, DOR, ETR, RPV, BIC, CAB, or EVG/c	**Not recommended**
	TAF	Use with caution[c] at dose indicated below.
	All other ARV drugs	10 mg/kg (usual dose 600 mg)
Rifabutin[a] **Note:** DOR and RPV[d] doses need to be adjusted when used with rifabutin.	PI with COBI, TAF, RPV (IM), BIC, CAB, EVG/c-containing regimens	**Not recommended**
	DTG, RAL, DOR, EFV, or RPV (PO only[d])	5 mg/kg (usual dose 300 mg)
	HIV PIs with RTV	150 mg daily[e]
	EFV	450–600 mg

Key: ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; IM = intramuscular; MVC = maraviroc; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TB = tuberculosis

HIV-TB treatment guidelines

Rifapentine and Dolutegravir are safe

- DOLPHIN trial:
  - Phase ½ single arm trial (total of 50 individuals)
  - 50 mg of daily dolutegravir in place of efavirenz for 8 weeks, then 12 doses once weekly INH-rifapentine
  - Followed 4 weeks after completion of treatment. HIV viral loads were measured at baseline and at weeks 11 and 24.
  - Viral loads less than 40 copies/mL at weeks 11 and 24.

- Dooley, KE et al. Lancet HIV 2020 Jun;7(6):e401-e409

Recommended regimens for co-treatment of HIV-TB

- Dolutegravir (DTG) + 2 nucleosides or Raltegravir (RAL)
  - Dolutegravir of 50mg BID with rifampin
  - Raltegravir to 800mg BID with rifampin
- Do not use elvitegravir, cabotegravir (IM or PO) or bictegravir-containing regimens
- 2nd line: Efavirenz + 2 nucleosides
- Rifabutin-based TB treatment
  - Alternative when PI class needed
  - Can be used with DTG or RAL with no dose adjustment
  - Could use oral rilpivirine if dose is increased to 50mg daily
- Rifapentine
  - efavirenz, raltegravir, or once-daily dolutegravir-based ARV regimen

Timing of ART in patients with TB (who have started TB treatment)

- Always treat TB before initiating ART whenever possible
- CD4 count cut points are at the time of diagnosis of TB
- Advanced AIDS (CD4 < 50): immediate ART (within 2 weeks) improves survival
  - Markedly increased risk of IRIS, including fatal IRIS events
  - Overall survival benefit despite IRIS
- CD4 > 50: early ART (~ 2 months) provides good balance of competing risks of death/AIDS vs. IRIS
- Caveats
  - CNS involvement – no benefit to immediate therapy, and there may be increased risk

- CAMELIA-NEJM 2011
- STRIDE-NEJM 2011
- SAPiT-NEJM 2010, 2011
- TB-HAART, Lancet-ID 2014

Adverse events in treatment of HIV and TB

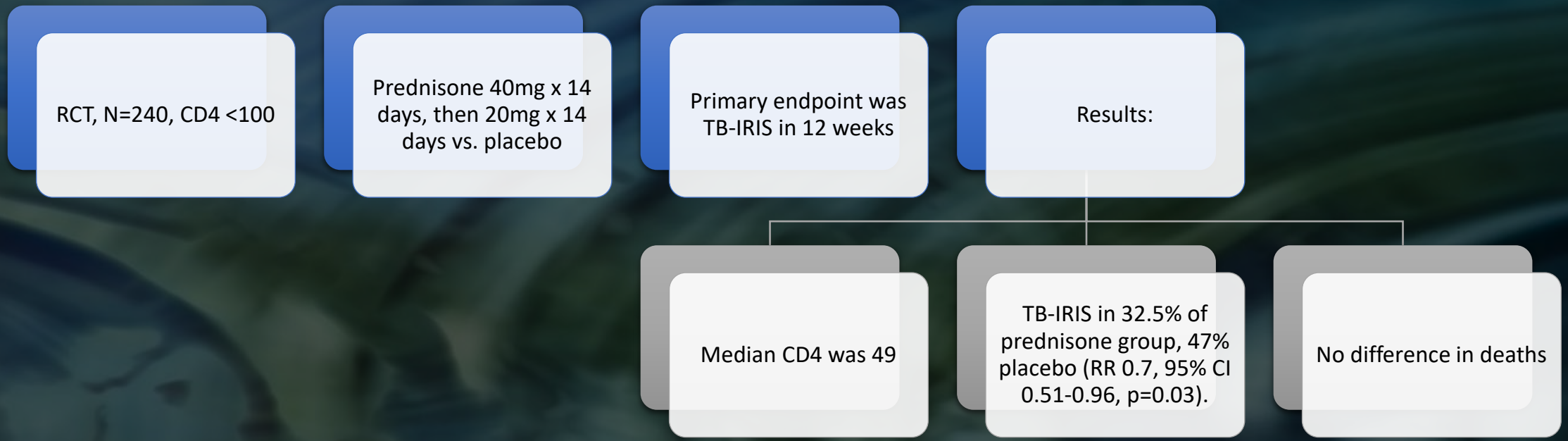
- GI intolerance, rash, hepatotoxicity
- IRIS
  - Paradoxical worsening after clinical improvement
  - Unmasking of another opportunistic infection
- Addition of TB treatment to ART may not be associated with increased risk of adverse events
  - Data comparing adverse events from TB-HAART and other trials (CAMELA, SAPiT, STRIDE)
    - similar rates of adverse events during anti-TB therapy with and without concomitant ART
    - Suggests that adding in ART does not increase risk of adverse events

- Mycobacterium tuberculosis Infection and Disease | NIH (hiv.gov)

Types of immune reconstitution inflammatory syndrome (IRIS) events in HIV-TB

- Fevers
- New or worsening adenitis
- New or worsening pulmonary infiltrates
- New or worsening pleuritis, pericarditis, or ascites
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepatosplenomegaly, soft tissue abscesses

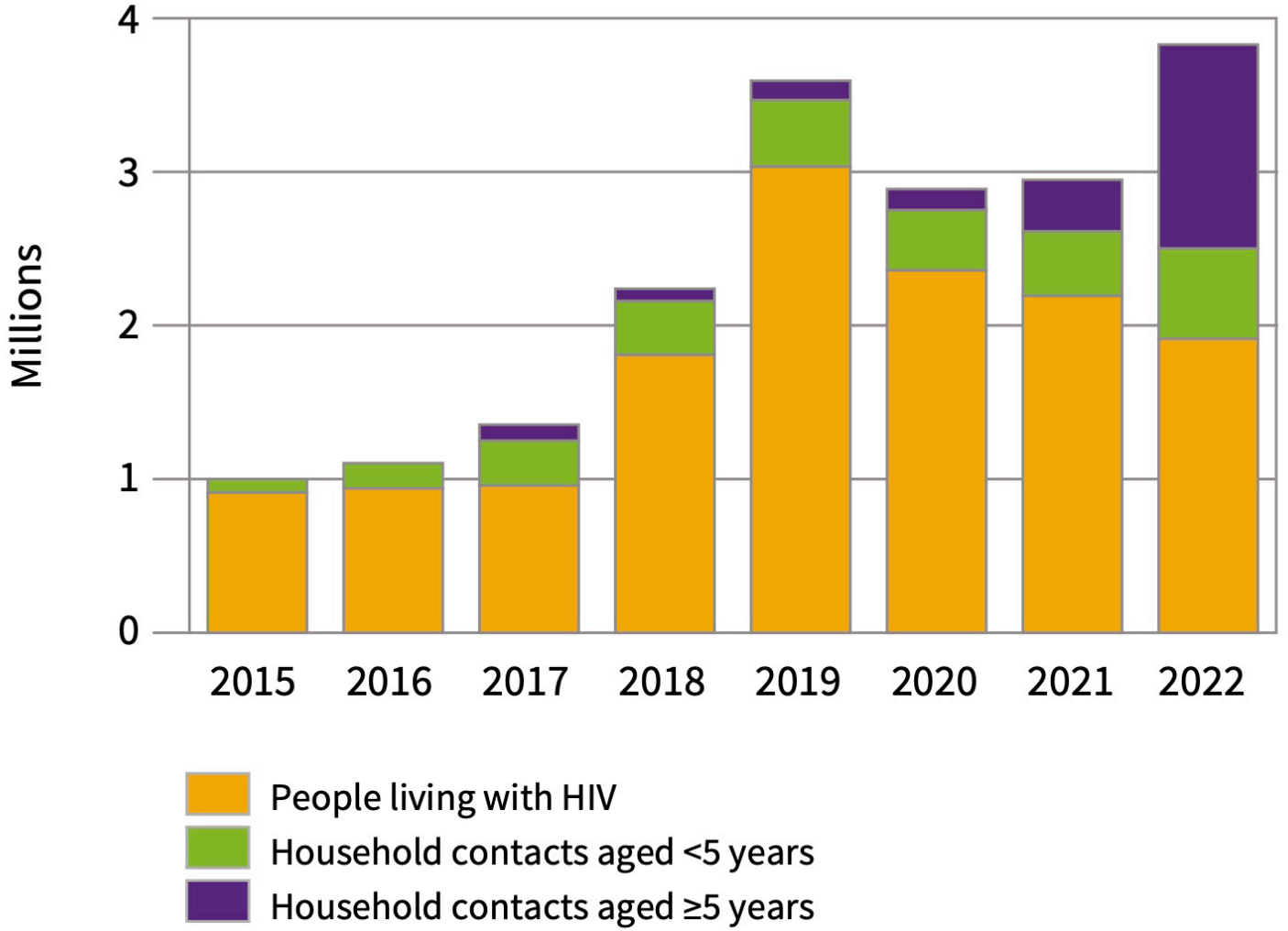
Initiation of ART+ prednisone reduces IRIS risk in HIV-TB for people with low CD4 counts



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

Treatment of LTBI

The global number of people provided with TB preventive treatment, 2015–2022



Recommended LTBI regimens for people *without* HIV

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
		Conditional	Low (HIV positive)
Alternative	6 mos isoniazid given daily	Strong§	Moderate (HIV negative)
		Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

Abbreviation: HIV = human immunodeficiency virus.

* *Preferred:* excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens and therefore higher effectiveness; *alternative:* excellent efficacy but concerns regarding longer treatment duration, lower completion rates, and therefore lower effectiveness.

† No evidence reported in HIV-positive persons.

§ Strong recommendation for those persons unable to take a preferred regimen (e.g., due to drug intolerability or drug-drug interactions).

Belknap, R. MMWR 2020

Recommended LTBI regimens for people Living with HIV

LTBI treatment	Regimen	Notes
first line	INH + rifapentine once weekly for 12 doses	efavirenz, dolutegravir, raltegravir based regimens
second line	INH + rifampin daily x 3 months	check drug-interactions with rifampin
Alternative #1	rifampin daily x 4 months	check drug-interactions with rifampin
Alternative #2	INH daily + B6 for 9 months	WHO recommends 6 months of INH
Not recommended by CDC or NTCA	INH+ rifapentine daily x 4 weeks	efavirenz based regimens only.
drug resistant LTBI	consult with public health/other experts	

Isoniazid and Rifapentine (3HP) both once weekly for 12 doses

- Isoniazid: 15 mg/kg, rounded up to the nearest 50 or 100 mg; 900 mg maximum
- Rifapentine
  - 10 to 14 kg: 300 mg
  - 14.1 to 25 kg: 450 mg
  - 25.1 to 32 kg: 600 mg
  - 32.1 to 49.9 kg: 750 mg
  - >50 kg: 900 mg maximum

Isoniazid with rifapentine (3HP)

- Adverse effects
  - Dyspepsia
  - Nausea/vomiting
  - Fatigue
  - Flu-like illness
  - Headaches
  - Hepatotoxicity
  - Rash

- Drug interactions—some overlap with rifampin
  - Hormonal anti-contraceptives
  - Coumadin
  - Antihypertensives
  - Antiretrovirals

Isoniazid and Rifapentine monitoring

- Obtain LFTs:
  - if aged >35
  - HIV
  - has underlying liver disease
  - pregnant/or within 3 months post-partum
  - Regular EtOH consumption or taking other hepatotoxic agents
- Safe in the following situations:
  - Not yet on ART
- Likely safe:
  - ART with efavirenz
  - ART with raltegravir
  - ART with dolultegravir
- Not recommended
  - Bictegravir
  - Boosting agents

Evidence for use of 3 months of daily isoniazid with rifampin (3HR) in PWHIV

- No difference in the incidence of TB disease comparing 3HR to 6-9 months of daily INH
- Hepatotoxicity less frequent with 3HR,
- Other adverse effects were more common with 3HR compared to daily INH and could lead to treatment discontinuation
- Monitoring similar to 3HP
- Weight based dosing similar to active TB treatment

Whalen CC, et al. NEJM 1997 Sep 18;337(12):801-8.
Rivero A et al. Inferm Infecc Microbiol Clin. 2007 May;25(5):305-10.
Johnson JL et al. AIDS 2001 Nov 9;15(16):2137-47

Rifampin daily for 4 months (usual dose is 600mg daily)

- Adverse effects
  - Dyspepsia
  - Orange discoloration to body fluids
  - Rash
  - Thrombocytopenia
  - Rare: neutropenia, hemolytic anemia, thrombocytopenia

- Drug interactions
  - ART
  - Hormonal anti-contraceptives
  - Coumadin
  - Thyroid hormone
  - Anti-seizure agents
  - Antihypertensives
  - Antipsychotics
  - Plus many more

Rifampin—monitoring

- Check baseline labs if:
  - HIV-positive
  - History of liver disease
  - Regular alcohol use
  - Age >50
  - Pregnant or post-partum (within 3 months)
  - On hepatotoxic medications
- Labs during follow-up only if baseline labs elevated or symptomatic
- Monthly follow-up recommended

INH ADVERSE EVENTS

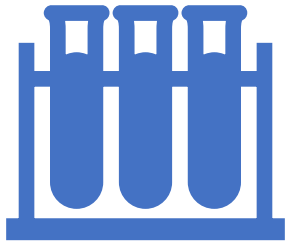
- Neurologic - interference in vitamin B_6 absorption
  - Higher risk in DM, renal insufficiency, alcoholism, malnutrition, HIV, pregnancy, seizure disorder
- GI
  - Hepatotoxicity
  - Nausea/vomiting
- Skin rash
- Drug interactions—always check!

Offer B6 at 25-50mg daily to individuals at higher risk for peripheral neuropathy, or can do 100mg weekly if on 3HP

Isoniazid: monitoring

- Check baseline labs if:

  - Living with HIV
  - History of liver disease
  - Regular alcohol use
  - Age >35
  - Pregnant or post-partum (within 3 months)
  - H/o injection drug use
  - On hepatotoxic medications



Labs during follow-up only if baseline labs elevated or symptomatic

Monthly follow-up recommended

ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279

- Phase 3 RCT, open-label, 10 countries participating, n=3,000
  - >13 years, living in high TB-burden areas OR who were TST/IGRA positive
  - ART with efavirenz or nevirapine; followed for 3 years
  - Randomized to 1HP* or 9H*
  - Primary endpoint: incidence rates of active TB, TB death or death from an unknown cause

- Results:
  - **634 (21%) had positive TST or IGRA**
  - Primary endpoint:
    - N=34 1HP arm; 35 9H arm, for incidence rates of 0.69/100 PY for 1HP and 0.72/100 PY for 9H (IR difference = -0.025, upper 95% CI: 0.31, Table).
    - TB incidence rates were higher among those with +TST/IGRA but not different between the two arms
  - Treatment completion was 97% with 1 HP vs. 90% in the 9H arm, $p<0.01$

*1HP=isoniazid/rifapentine daily x 4 weeks; 9H=isoniazid daily x 9 months

Swindells, S. et al. N Engl J Med 2019; 380:1001-1011

Summary – treatment of HIV-related TB: LTBI

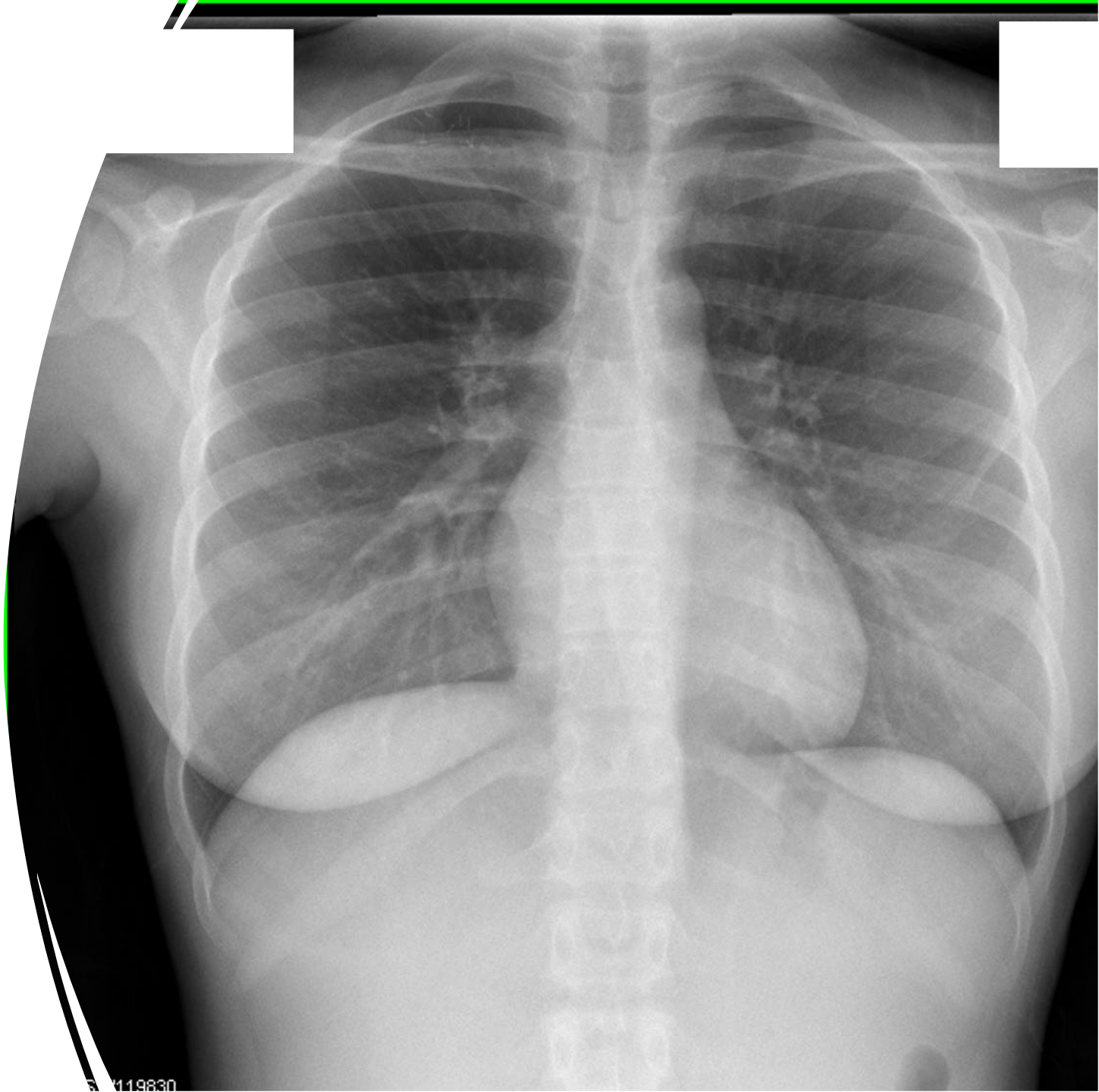
- All people with HIV should be screened for TB infection and offered treatment for LTBI
- Short course rifamycin-based regimens are preferred for people with HIV who need LTBI treatment
  - Shorter course regimens are better tolerated and are easier to complete
  - Most of the data are in INH-rifamycin combination regimens

Summary – treatment of HIV-related TB: issues with antiretroviral therapy

- HIV treatment initiated with consideration of the data that maximize benefit and lower risk of IRIS:
  - Less than 2 weeks if CD4 count is less than 50, then okay to wait and start within 2 months after starting active TB treatment if >50
    - Exceptions:
      - Considerations during pregnancy, transmission to partners
  - Preferred: dolutegravir or raltegravir-based with TDF+FTC or ABC+3TC
    - Still some limited role for PI/rifabutin combinations and efavirenz

Patient follow-up

- emtricitabine/tenofovir/efavirenz initiated
- TB treatment completed at 6 months
- Delivered a healthy baby who is HIV free



Questions?

Thank you!