TB and HIV

Lisa Armitige, MD, PhD

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TB Intensive
July 16 – 18, 2024
San Antonio, Texas

Lisa Armitige, MD, PhD has the following disclosures to make:

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

TB and HIV

Lisa Armitige, MD, PhD
Medical Consultant
Heartland National TB Center

Associate Professor
Internal Medicine/Pediatrics
University of Texas HSC at Tyler

Lisa Armitige, MD, PhD has the following disclosures to make:

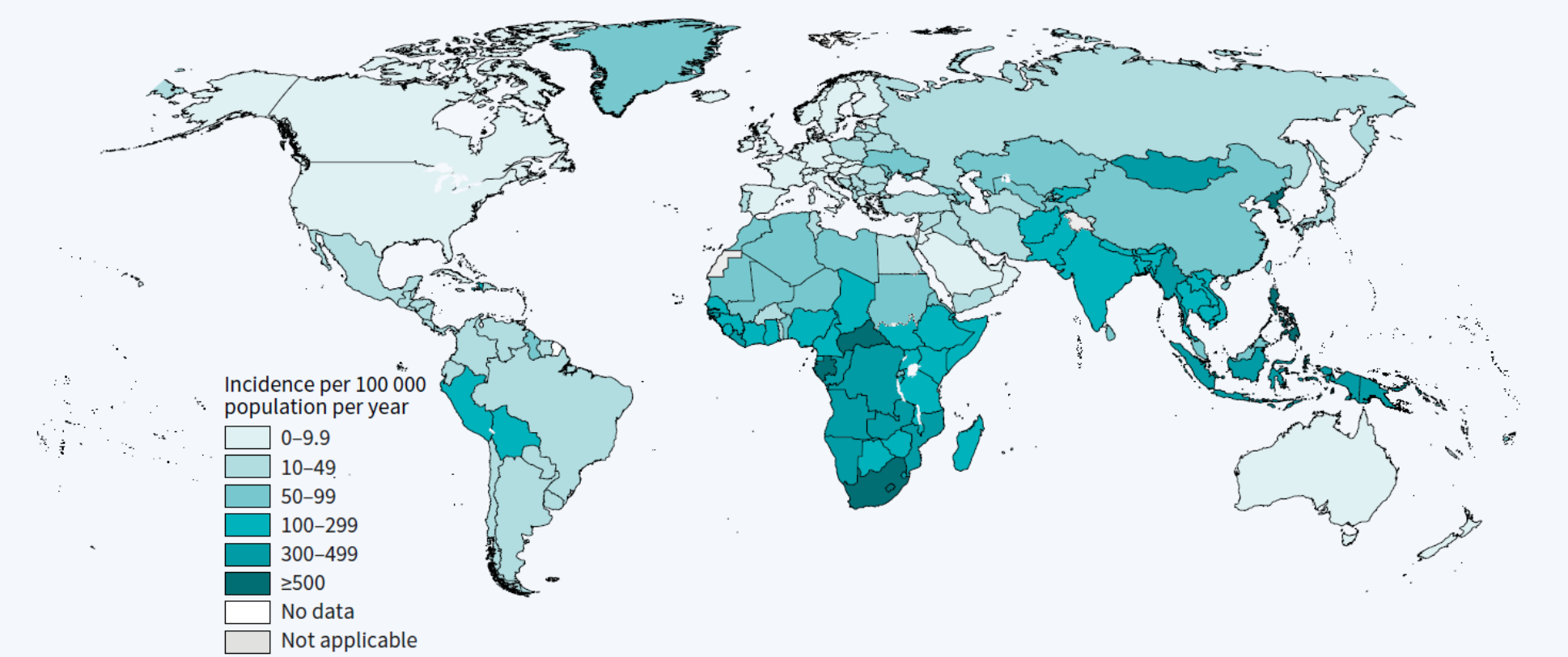
- Consultant for Oak Therapeutics

Epidemiology

Global Epidemiology of TB

FIG. 14

Estimated TB incidence rates, 2021

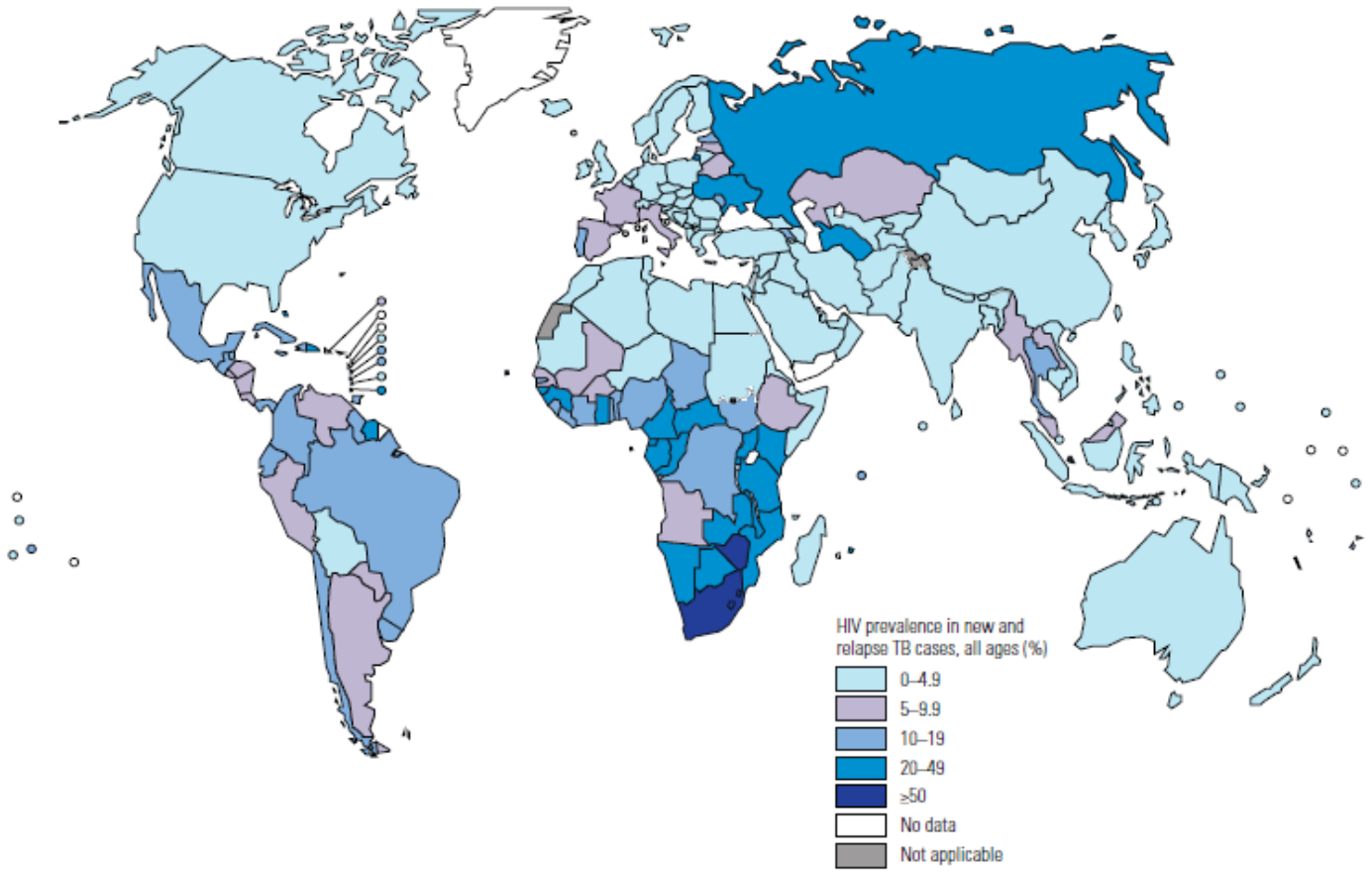


Global Tuberculosis Report 2022

Global Epidemiology of TB/HIV

FIG. 4.5

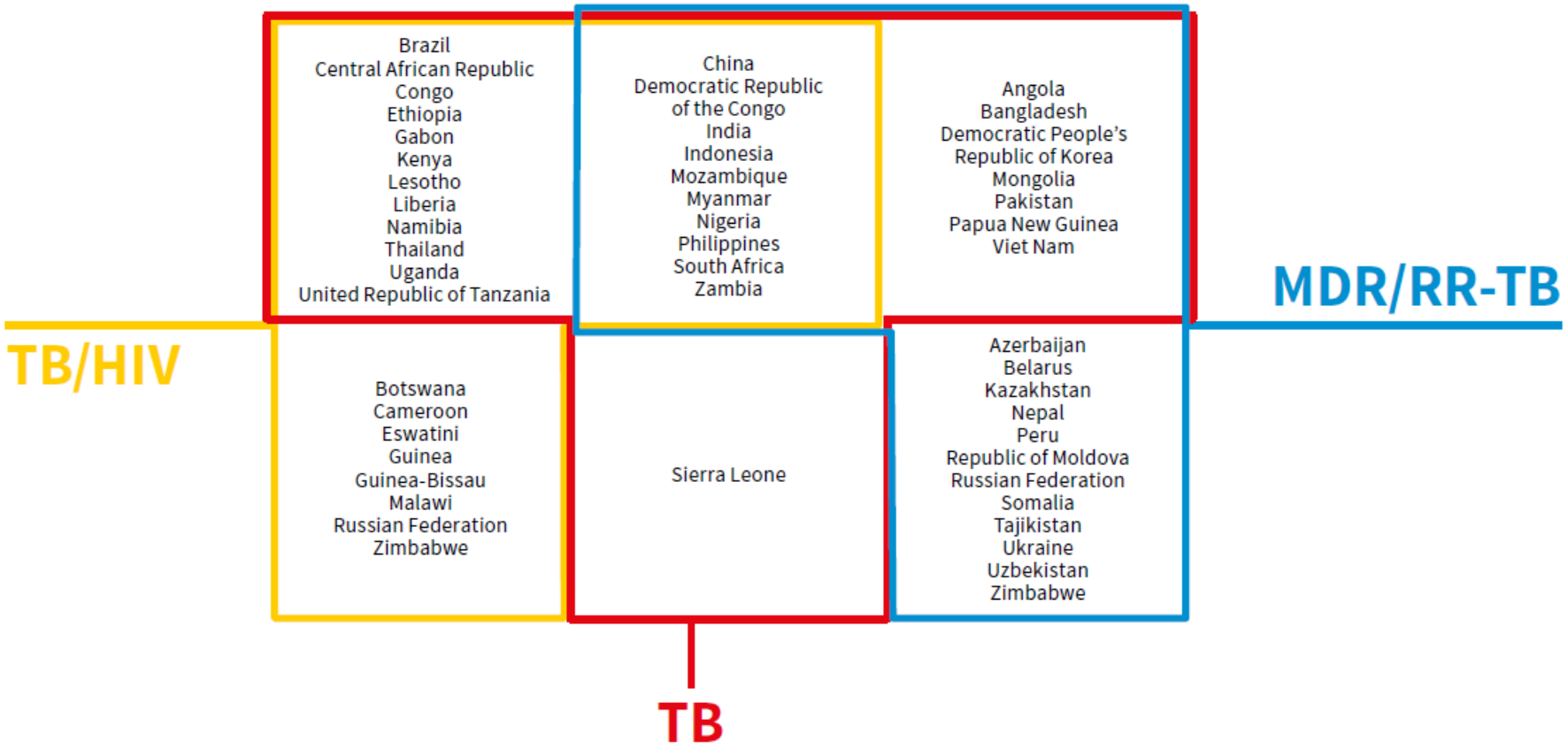
Estimated HIV prevalence in new and relapse TB cases, 2019



GLOBAL TUBERCULOSIS REPORT 2020

FIG. A3.1

The three global lists of high-burden countries for TB, HIV-associated TB and MDR/RR-TB to be used by WHO in the period 2021–2025, and their areas of overlap

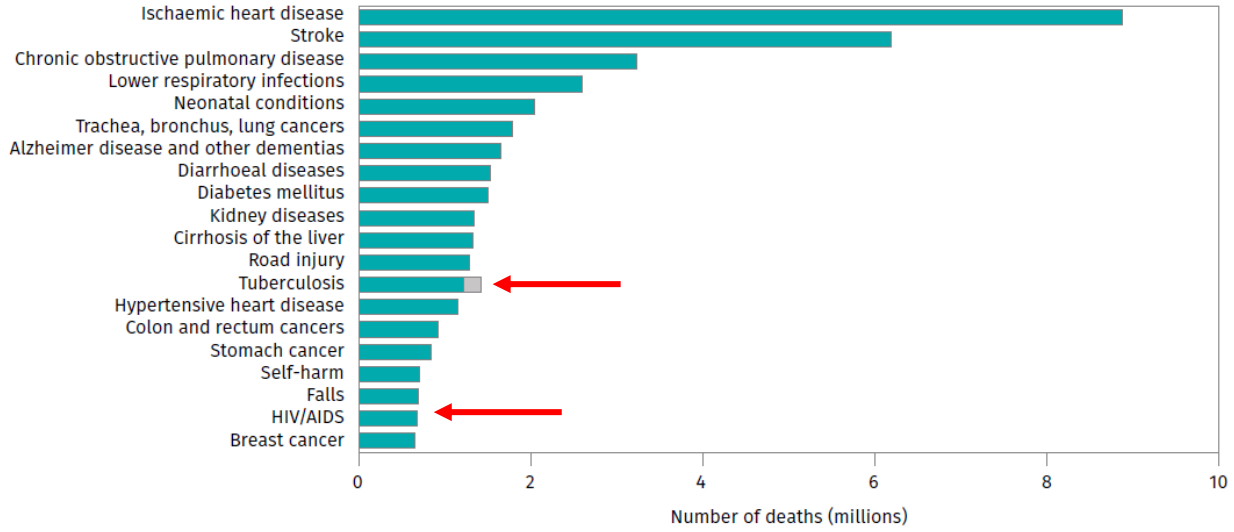


TB is a Greatest Infectious Killer Worldwide

FIG. 7

Top causes of death worldwide in 2019[a,b]

Deaths from TB among HIV-positive people are shown in grey.



[a] This is the latest year for which estimates for all causes are currently available. See WHO estimates, available at https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death

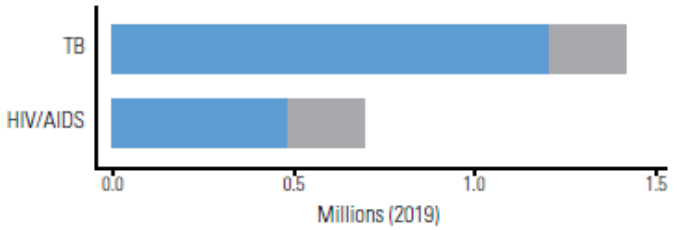
[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

Global Tuberculosis Report 2021

FIG. 4.15

Estimated number of deaths worldwide from TB and HIV/AIDS in 2019[a,b]

Deaths from TB among HIV-positive people are shown in grey.



[a] For HIV/AIDS, the latest estimates of the number of deaths in 2019 that have been published by UNAIDS are available at http://www.unaids.org/en/ (accessed 16 August 2020). For TB, the estimates for 2019 are those published in this report.

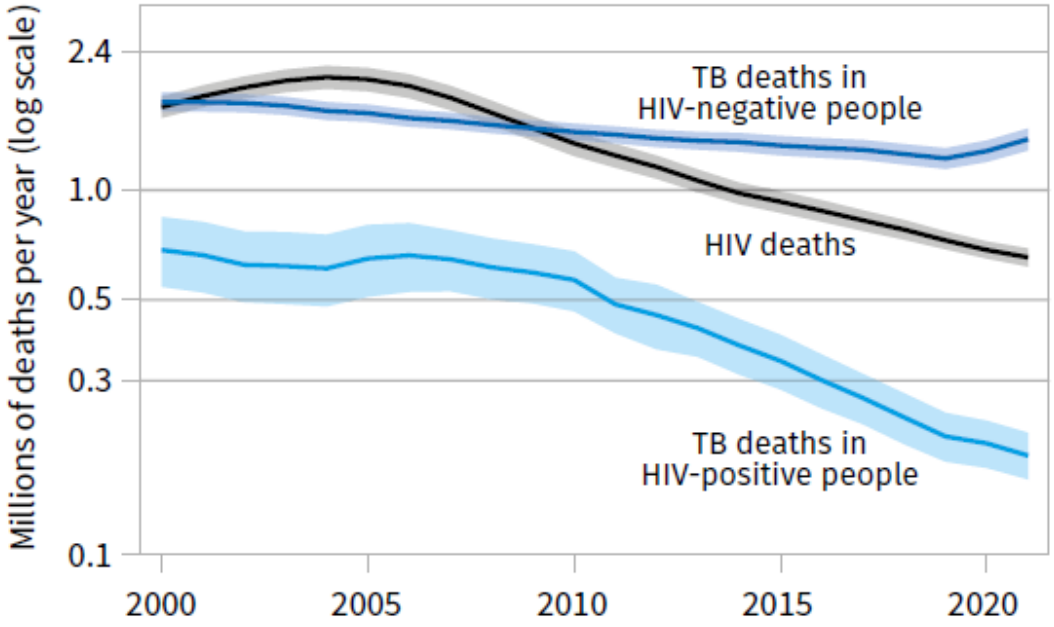
[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

Global Tuberculosis Report 2020

FIG. 7

Global trends in the estimated number of deaths caused by TB and HIV, 2000–2021[a,b]

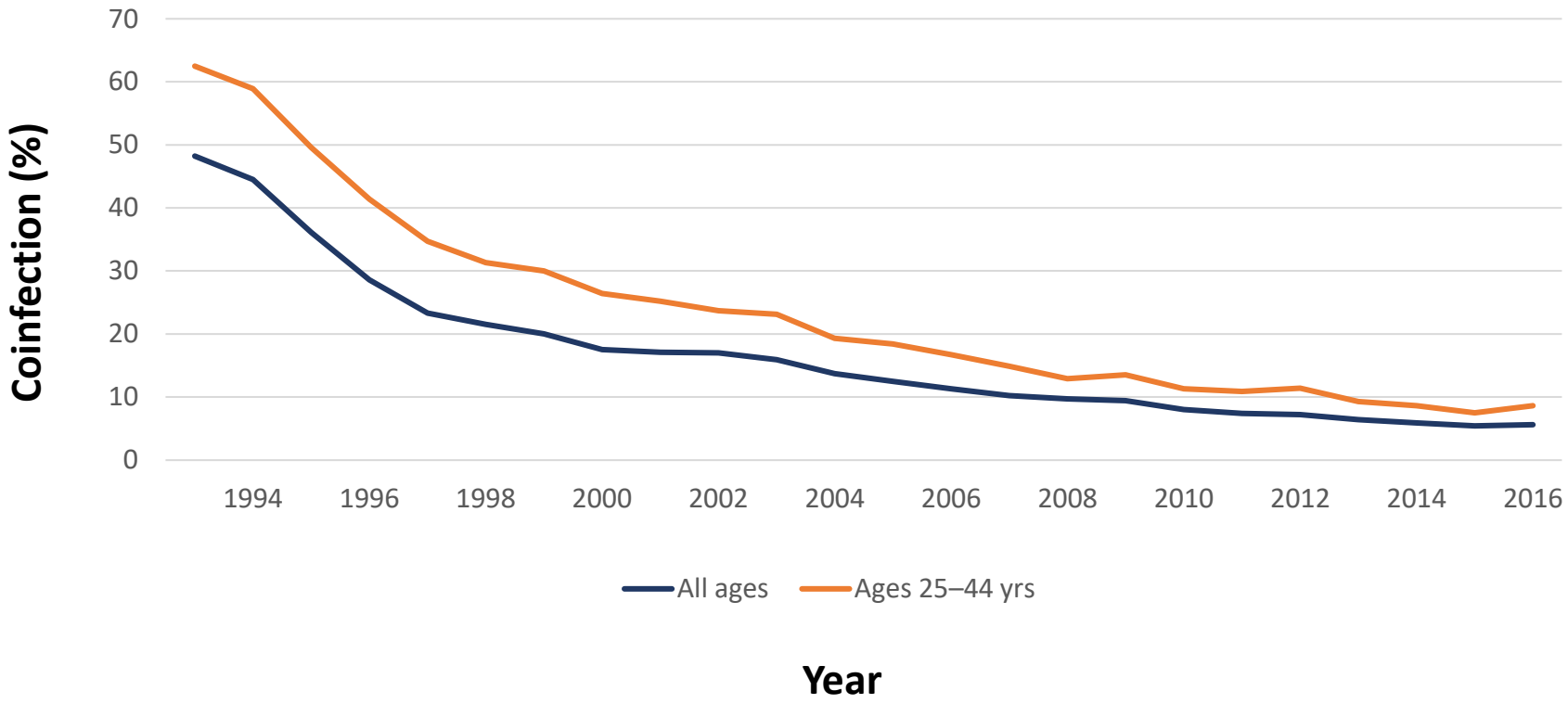
Shaded areas represent 95% uncertainty intervals.



[a] For HIV/AIDS, the latest estimates of the number of deaths in 2021 that have been published by UNAIDS are available at http://www.unaids.org/en/ (accessed 15 August 2022). For TB, the estimates for 2021 are those published in this report.

[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

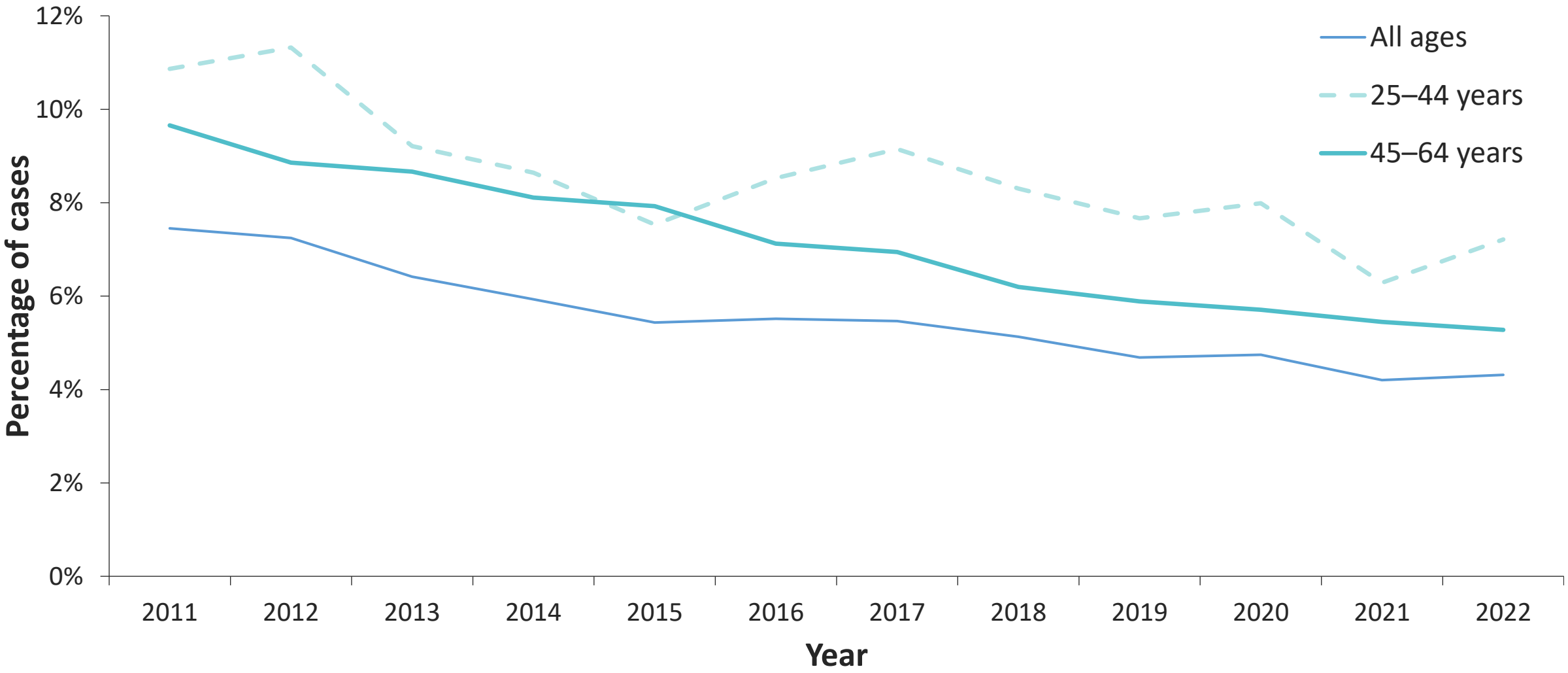
Estimated HIV Coinfection Among Persons Reported with TB, United States, 1993–2016*



* As of June 21, 2017.

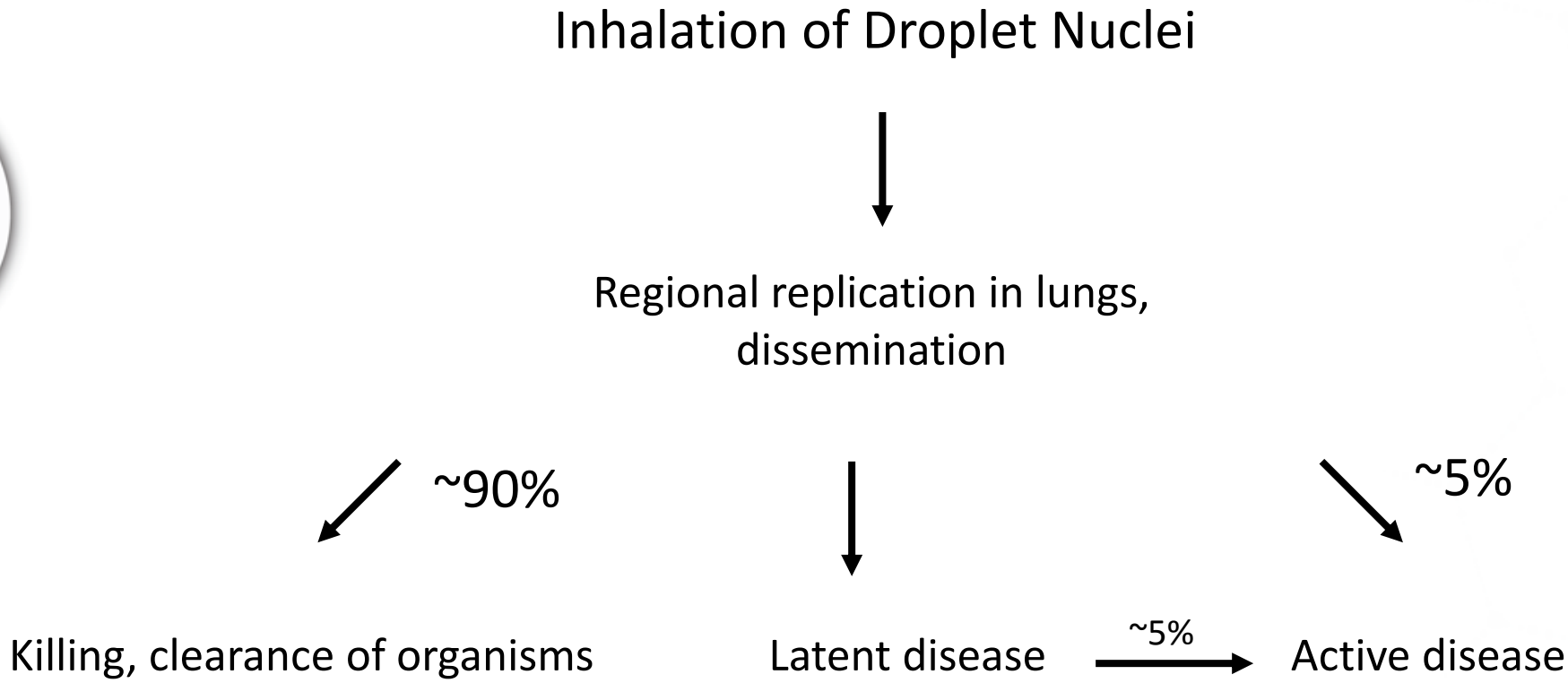
Note: Minimum estimates are based on reported HIV-positive status among all TB patients in the age group.

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

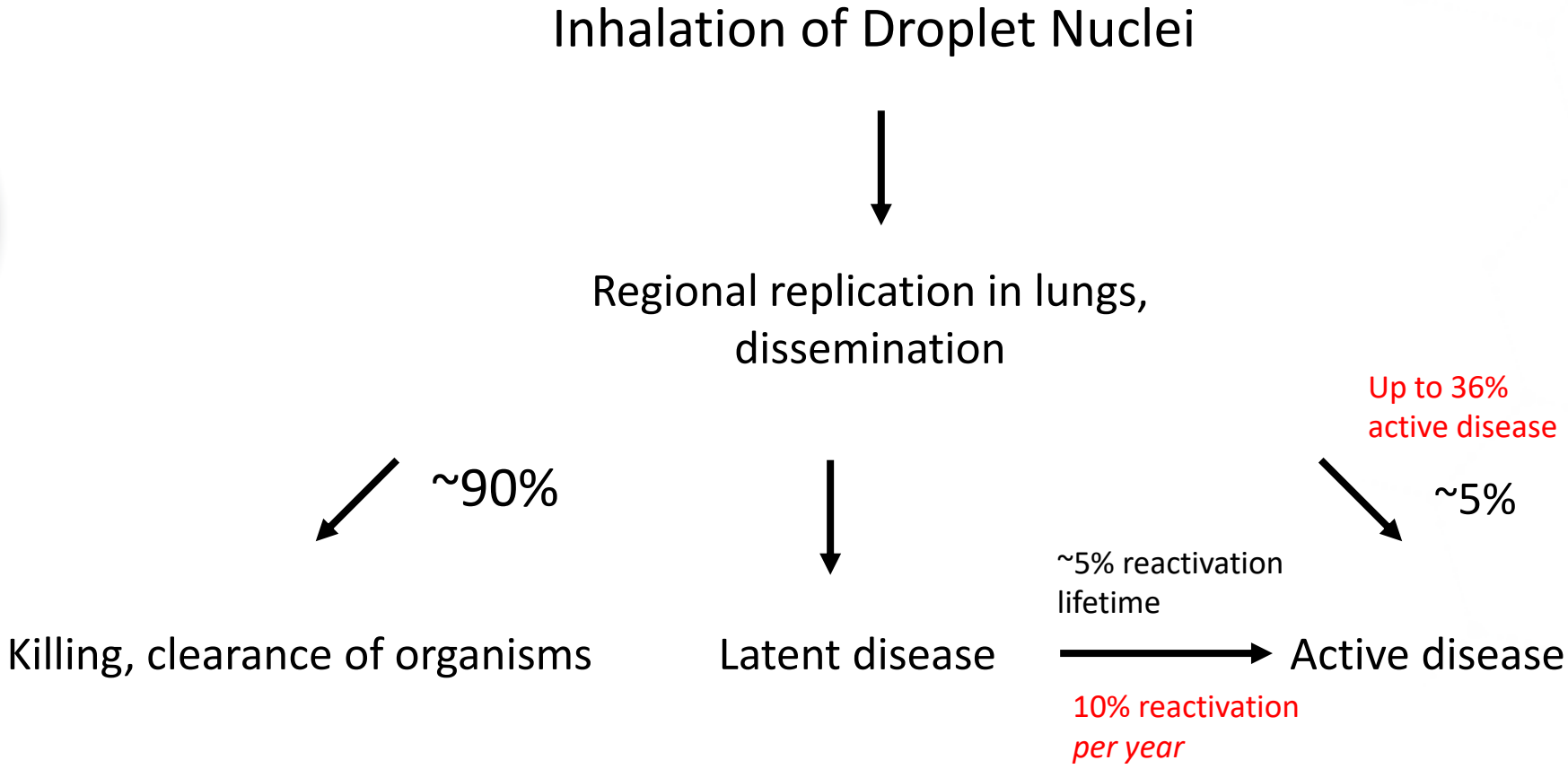


*Persons alive at diagnosis with HIV test results

Outcomes of Exposure to *M. tuberculosis*



Outcomes of Exposure to *M. tuberculosis* in HIV-negative and HIV-positive patients



Diagnosis of Tuberculosis in Persons Living with HIV

TB screening in PLWH

- All persons with HIV should be evaluated for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure **(AII).**

- Persons with advanced HIV infection (CD4 count <200 cells/mm^3) and negative diagnostic tests for LTBI should be retested for LTBI once they start ART and attain a CD4 count ≥200 cells/mm^3

- Annual testing for LTBI using TST or IGRA is recommended only for people with HIV who have a history of a negative test for infection and are at high risk for repeated or ongoing exposure to persons with active TB disease (targeted testing)

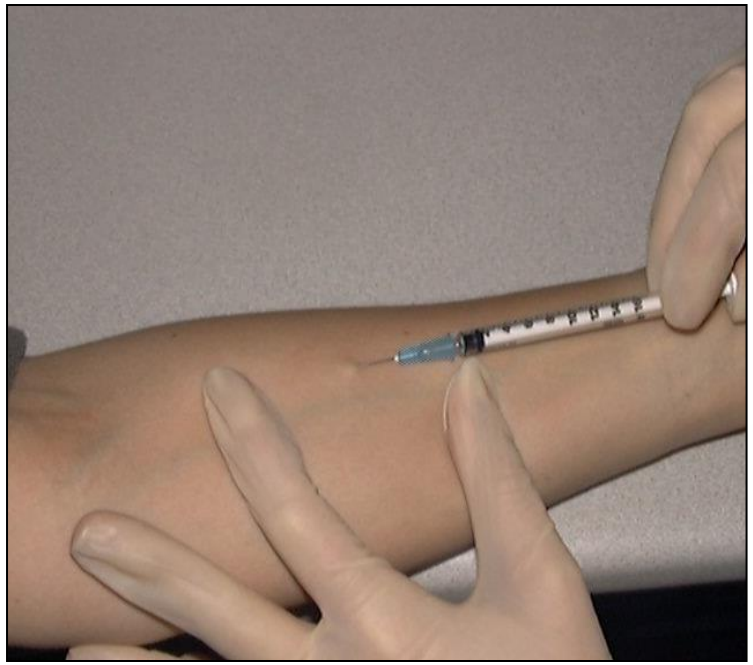
The Tuberculin Skin Test (TST)

- Where we started……

  100 years ago

- 0.1 ml of 5 TU PPD tuberculin injected intradermally

- Induration in millimeters read 48-72 hours after injection



Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

TST Limitations

- Technical problems in administration and reading
- >1 visit needed
- False-negative responses
  - Anergy (compromised immunity)
  - TST reversion at old age
- Repeated TSTs boost the immune response
  - Need 2-step approach in serial testing
- False positives
  - Nontuberculous mycobacteria (NTM)
  - Bacille Calmette-Guerin vaccination (BCG)

Diagnosis

Table 1. Bacteriological and histological results observed during HIV-associated TB as a function of immune status

	CD4 < 200/mm^3	CD4 > 200/mm^3	References
Positive tuberculin skin test reaction (> 5 mm without BCG)	30% *	50% *	[23]
Acid-fast bacilli on smear	56–60%	50–58%	[22,23,25]
Acid-fast bacilli on biopsy	60–65%	50–56%	[22]
Granuloma in biopsy	60–75%	67–100%	[23,31,32]
Mycobacteraemia	20–49%	0–7%	[22,30]

Clinical Microbiology and Infection, Volume 10 Number 5, May 2004

Infection (2022) 50:597–606
https://doi.org/10.1007/s15010-022-01789-9

REVIEW

Diagnostic accuracy of the interferon-gamma release assay in acquired immunodeficiency syndrome patients with suspected tuberculosis infection: a meta-analysis

Hao Chen[1] · Atsushi Nakagawa[2] · Mikio Takamori[3] · Seitarou Abe[4] · Daisuke Ueno[5] · Nobuyuki Horita[6] · Seiya Kato[7] · Nobuhiko Seki[1,8]

Received: 2 January 2022 / Accepted: 22 February 2022 / Published online: 6 March 2022

- 45 articles, 6,525 PLWHIV (2661 with active disease, 806 with LTBI)
- QFT sensitivity/specificity 0.663/0.867
- Tspot sensitivity/specificity 0.604/0.862
- Sensitivity of IGRAs in diagnosing LTBI was 0.64

Signs & Symptoms - Pulmonary TB

Pulmonary Symptoms:

- Productive, prolonged cough of over 3 weeks duration
- Chest pain
- Hemoptysis

Systemic Symptoms:

- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability

Testing for TB Infection

- Clients who have a + TST result, a positive IGRA result or symptoms suggestive of TB (regardless of TST/IGRA results) *should be evaluated with a chest x-ray*

- Patients with HIV who may not react to testing by TST or IGRA should have a chest x-ray if TB is suspected or if exposed to an active TB case

- If abnormalities are noted, or the client has symptoms suggestive of extrapulmonary TB, additional diagnostic tests should be conducted

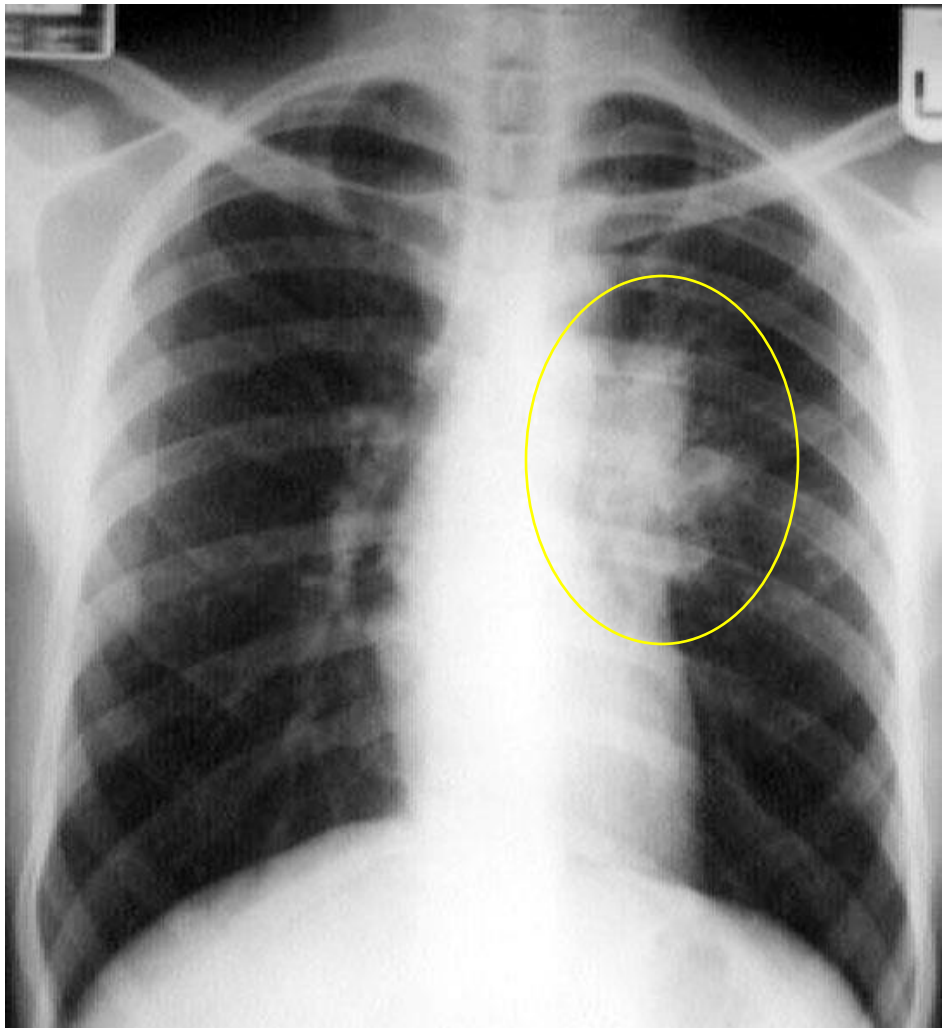
CXR – HIV infected persons

In HIV-infected persons almost any abnormality on CXR may indicate TB

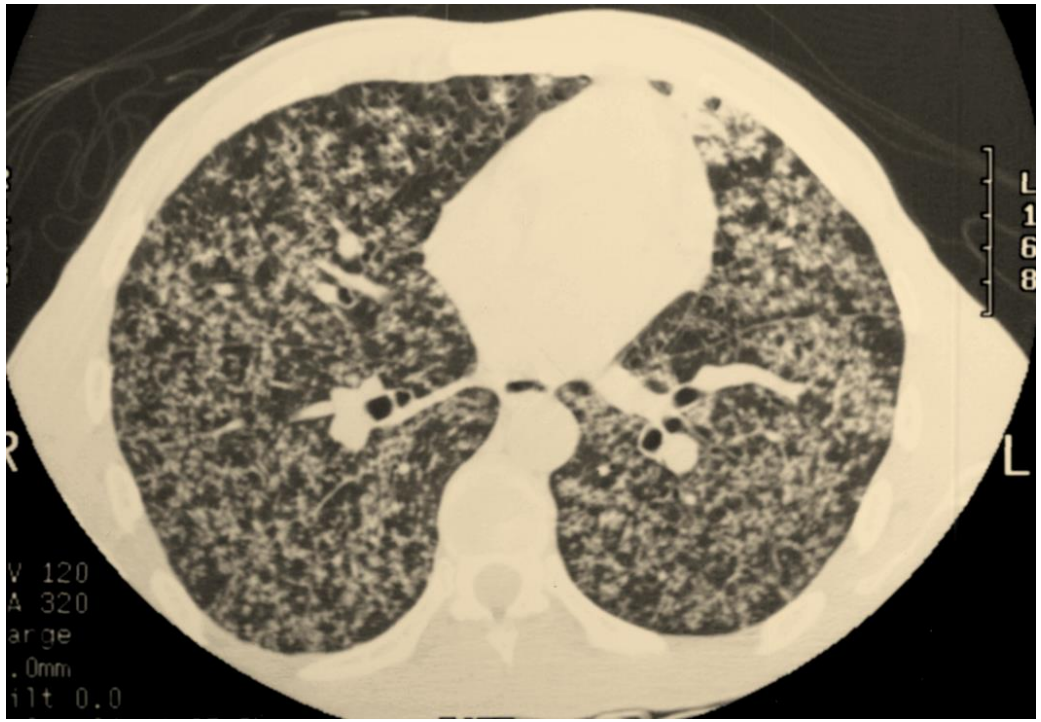
- May cause infiltrates without cavities in any lung zone
- May cause mediastinal or hilar lymphadenopathy

  with or without infiltrates or cavities

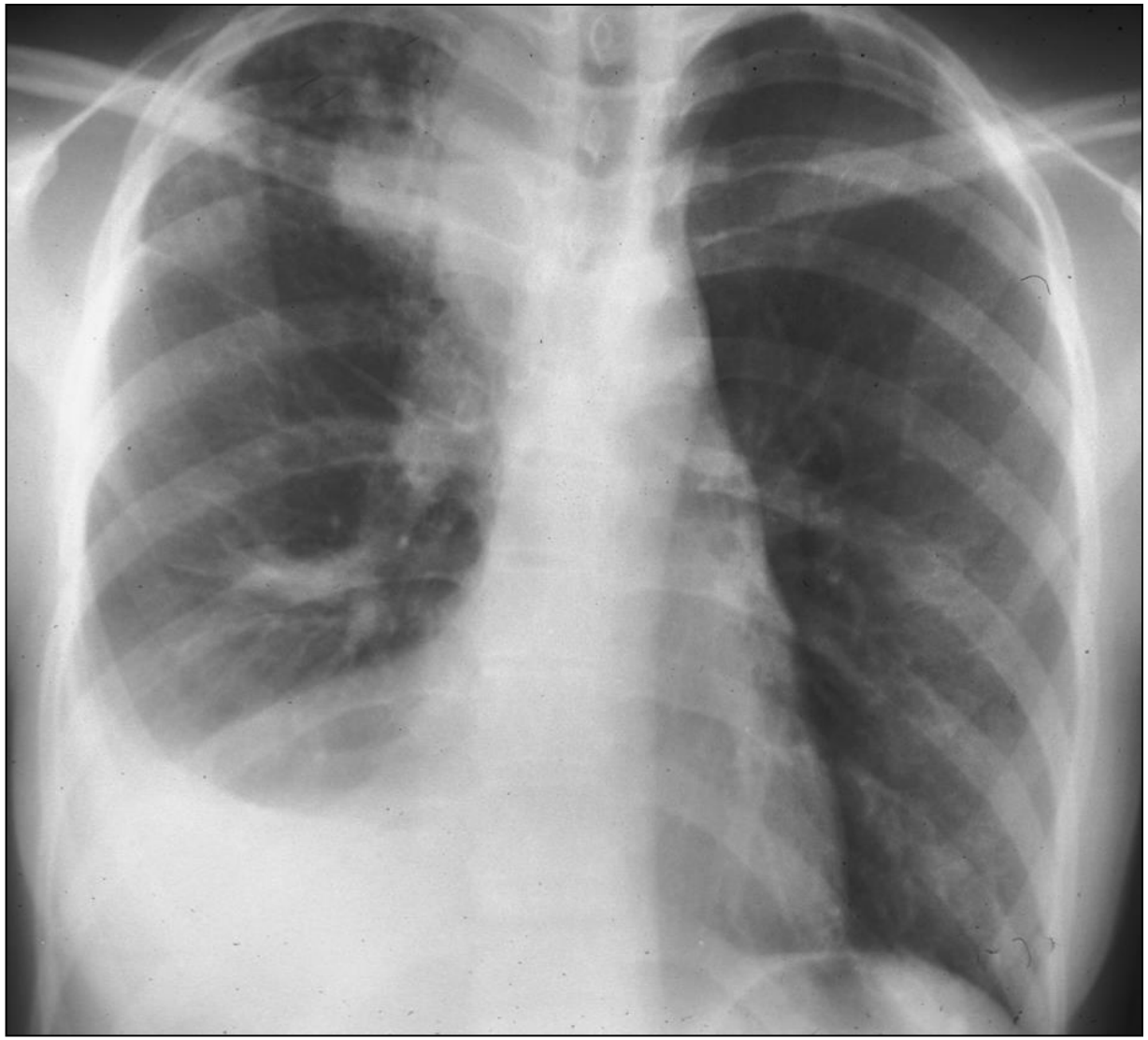
Primary Tuberculosis



Miliary tuberculosis



Tuberculosis and HIV



Screening for pulmonary tuberculosis in HIV-infected individuals: ACTG Protocol A5253

IJTLD 17(4): 532-9, 2013

- Comparison of evaluation tools for diagnosis of TB in HIV patients
  - SOC screening algorithm: cough, fever, weight loss, night sweats in previous 30 days, sputum smear, CXR (if not pregnant)
  - Enhanced screening tool added other symptoms to screening (GI, GU, neuro, derm) and fluorescent microscopy
- 801 patients, average 33 y/o, median CD4 275
- Results:
  - 51% with TB had a normal CXR
  - SOC sensitivity 54%, specificity 76%, PPV 24%, NPV 92%
  - Cough was the most sensitive symptom (especially when combined with abnl CXR, LN, or CD4 count < 200)
  - Only 6 of 54 (11.1%) with positive TB culture had positive smear

An Algorithm for Tuberculosis Screening and Diagnosis in People with HIV

N Engl J Med 2010;362:707-16.

Appendix Table 1. Smear and culture results of patients with TB (N=267), stratified by symptoms and chest radiograph result.

Category		Enrolled patients, n	TB diagnosed, n (% of enrolled patients)	Positive acid-fast smear, n (% of TB diagnosed)	Number of positive cultures, n (% of TB diagnosed)	
Symptoms*	Chest radiograph				1	>1
Absent	Normal	493	7 (1)	0	5 (71)	2 (29)
Present	Normal	865	87 (10)	26 (30)	40 (46)	47 (54)
Absent	Abnormal	56	11 (20)	3 (27)	2 (18)	9 (82)
Present	Abnormal	334	162 (49)	92 (57)	21 (13)	140 (87)

*Any one of: any cough in the past 4 weeks, any fever in the past 4 weeks, or night sweats for ≥3 weeks.

Evaluation of the Xpert MTB/RIF Assay at a Tertiary Care Referral Hospital in a Setting Where Tuberculosis and HIV Infection Are Highly Endemic

Clinical Infectious Diseases 2012;55(9):1171–8

Justin O'Grady,[1,2,a] Matthew Bates,[1,2,a] Lophina Chilukutu,[2] Judith Mzyece,[2] Busiku Cheelo,[2] Moses Chilufya,[2] Lukundo Mukonda,[2] Maxwell Mumba,[2] John Tembo,[2] Mumba Chomba,[2] Nathan Kapata,[2,3] Markus Maeurer,[4] Andrea Rachow,[5] Petra Clowes,[5] Michael Hoelscher,[5,6] Peter Mwaba,[2,7] and Alimuddin Zumla[1,2]

[1]Department of Infection, University College London Medical School, Royal Free Hospital, United Kingdom; [2]University of Zambia and University College London Medical School Research and Training Programme, University Teaching Hospital, [3]National Tuberculosis Control Programme, Lusaka, Zambia; [4]Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, Stockholm, Sweden; [5]Mbeya Medical Research Programme, Tanzania; [6]Department for Infectious Diseases and Tropical Medicine, Klinikum of the University of Munich, Germany; and [7]Ministry of Health, Lusaka, Zambia

- All patients who could produce a sputum screened
- 881 patients enrolled, 70.9% HIV positive
- Culture confirmed TB in 201
- Persons with HIV (with culture proven TB):
  - 88.2% sensitivity overall
  - 74.7% sensitive in smear negative, culture + specimens

Bacteriologic or histologic exam

- Sputum
  - Three (8-24 hours apart, at least one first thing in the morning)
- Tissue
  - Lymph node biopsy
  - Bone marrow biopsy
- Other specimens
  - Urine
  - CSF
  - Peritoneal fluid
  - Pleural fluid (pleural biopsy)

Diagnosis – Summary

- Requires a high index of suspicion and must utilize many pieces of information in making the diagnosis
- TB can present very differently in HIV-infected patients when compared to HIV-negative patients
- The most effective tool in diagnosing TB disease in PLWH is an astute physician.

~~Latent~~ TB Infection (LTBI)

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

HIV-infected persons, regardless of age, should be treated for LTBI *if they have no evidence of active TB* and exhibit the following characteristics:

- 1) a positive diagnostic test for LTBI and no prior history of treatment for active or latent TB (AI);
- 2) a negative diagnostic test for LTBI but are close contacts of persons with infectious pulmonary TB (AII); and
- ~~3) a history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for LTBI (AII)~~

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

Initiating Treatment for LTBI

Before initiating treatment for LTBI

- Rule out TB disease
  - i.e. wait for culture results if specimen obtained
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy

TB Infection Treatment Options

- CDC Recommended Treatment regimens:
  - INH/Rifapentine x 3 months (3HP)
    - Once weekly DOT x 12 weeks
    - Average of 10 pills at once
  - Rifampin (or rifabutin) x 4 months
    - Daily (10 mg/kg: 600 mg max)
  - INH/rifampin x 3 months
    - Same doses as INH and rifampin monotherapies
  - INH x 6-9 months
    - Daily (5 mg/kg: 300 mg max) or BIW (15 mg/kg: 900 mg max)

MMWR / February 14, 2020 / Vol. 69 / No. 1

3 HP weekly for treatment of M. tuberculosis infection in HIV co-infected persons:

TBTC Study 26 ACTG 5259; AIDS Sterling et al. June 2016

- 3 HP by DOT vs. 9 months of daily INH in HIV-infected persons.
- Median baseline CD4+ counts were 495 and 538 in the 3HP and 9 INH arms (P = 0.09)
- In the modified intention to treat analysis:
- 2 TB cases among 206 persons in the 3HP arm
- 6 TB cases among 193 persons in the 9H arm.
- **Cumulative tuberculosis rates were: 1.01% vs. 3.50% in the 3HP and 9H arms**
- **Treatment completion was higher with 3HP (89%) than 9H (64%)** (P < 0.001)
- Drug discontinuation due to an adverse reaction was similar (3% vs. 4%); (P = 0.79)
- **Conclusions:** Among HIV-infected persons with median CD4+ count of approximately 500 cells/mm3, **3HP was as effective and safe for treatment of latent M. tuberculosis infection as 9H, and better tolerated.**

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

N Engl J Med 2019; 380:1001-1011

- 3000 enrollees, 45 sites,10 countries followed for 3 years, half on ART (efavirenz or nevirapine) at entry
- Multicenter, randomized, open-label, phase 3 trial enrolled individuals with HIV >13 y/o living in high TB-burden areas or evidence of LTBI.
- 1 month of daily H 300 mg plus P 450-600 mg (1HP) or 9 months daily H 300 mg (9H), and followed until 3 y after the last enrollment.
- Primary end points: active TB, TB death, or death from an unknown cause.
- Median CD4 count was 470 cells/mm^3 (IQR 346-635) , 634 (21%) had positive TST or IGRA.

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

N Engl J Med 2019; 380:1001-1011

- The primary endpoint
  - 32/1488 pts (2%) in the 1HP arm and 33/1488 (2%) in the 9H arm
  - Serious adverse events occurred in 5.6% of 1HP pts and 7.1% of 9H pts (p=0.1).
  - Treatment completion was higher in the 1HP arm than 9H (97% vs. 90%, P<0.01).
  - Probable or confirmed active TB: 24 cases in 1HP, 29 cases in 9H

- Once daily 1HP was
  - non-inferior to 9H,
  - had fewer adverse events
  - more likely to be completed in HIV-infected adults and adolescents.

Duration of Therapy

- INH
- Rifampin (or rifabutin)
- INH + rifampin
- INH +RPT

- 6-9 months (180-270 doses)
- 4 months (120 doses)
- 3 months (90 doses)
- 12 weeks (12 doses)

The longer the duration/more doses, the less likely your patient is to complete Rx!

Fewer than 60% complete 9 months of INH!

Treatment for Active TB

TB and HIV Co-infection: Treatment Principles

- The treatment of TB in patients with HIV infection should follow the same principles as for the treatment of persons without HIV infection
- Initiate TB treatment immediately
  - Directly observed therapy is strongly recommended
- Initiate or optimize ART
  - Concomitant therapy for both TB and HIV shown to reduce mortality
    - Low CD4 count is risk factor for mortality
    - IRIS more common if ART is initiated early in course of TB treatment, but not associated with mortality

Clinical Infectious Diseases Advance Access published August 10, 2016

Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

[1]University of California, San Francisco; [2]Johns Hopkins University, Baltimore, Maryland; [3]California Department of Public Health, Richmond; [4]McMaster University, Hamilton, Ontario, Canada; [5]National Jewish Health, Denver, Colorado; [6]World Health Organization, Geneva, Switzerland; [7]Tuberculosis Control Section, San Francisco Department of Public Health, California; [8]Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [9]Harvard Medical School, Boston, Massachusetts; [10]McGill University, Montreal, Quebec, Canada; [11]WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri Care and Research Institute, Tradate, Italy; [12]Tuberculosis Control Program, Seattle and King County Public Health, and University of Washington, Seattle; [13]Ethics Advisory Group, International Union Against TB and Lung Disease, Paris, France; [14]University of Florida, Gainesville; [15]Boston University, Massachusetts; [16]Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; [17]University of Sassari, Italy; and [18]Baylor College of Medicine, Houston, Texas

ATS recommendations for treatment of tuberculosis

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance. *	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior. *	Lesser

When should HIV treatment be started?

- Considerations
  - Treatment of HIV improves outcomes in patients with TB
    - Decreased death or relapse
  - Multiple medications with multiple potential toxicities that are overlapping

Initiation of ART in patients with HIV/TB

- In patients with CD4 counts ***<50 cells/mm^3***, ART should be initiated within 2 weeks of starting TB treatment **(AI)**

- In patients with CD4 counts ***≥50 cells/mm^3*** with clinical disease of major severity ART should be initiated within 2 to 4 weeks of starting TB treatment.
  - CD4 count 50 to 200 cells/mm3 **(BI)**
  - CD4 count >200 cells/mm3 **(BIII)**

- In patients with CD4 counts ***≥50 cells/mm^3*** who do not have severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 weeks of TB therapy initiation.
  - CD4 count 50 to 500 cells/mm3 **(AI)**
  - CD4 count >500 cells/mm3 **(BIII)**

http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

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Initiation of ART in patients with HIV/TB

- In patients with CD4 counts <50 cells/mm^3: Initiate ART as soon as possible, but within 2 weeks of starting TB treatment (AI).
- In patients with CD4 counts ≥50 cells/mm^3: Initiate ART within 8 weeks of starting TB treatment (AIII).
- In all HIV-infected pregnant women: Initiate ART as early as feasible, for treatment of maternal HIV infection and to prevent mother-to-child transmission (MTCT) of HIV (AIII).
- In patients with tuberculous meningitis: Caution should be exercised when initiating ART early, as high rates of adverse events and deaths have been reported in a randomized trial (AI).

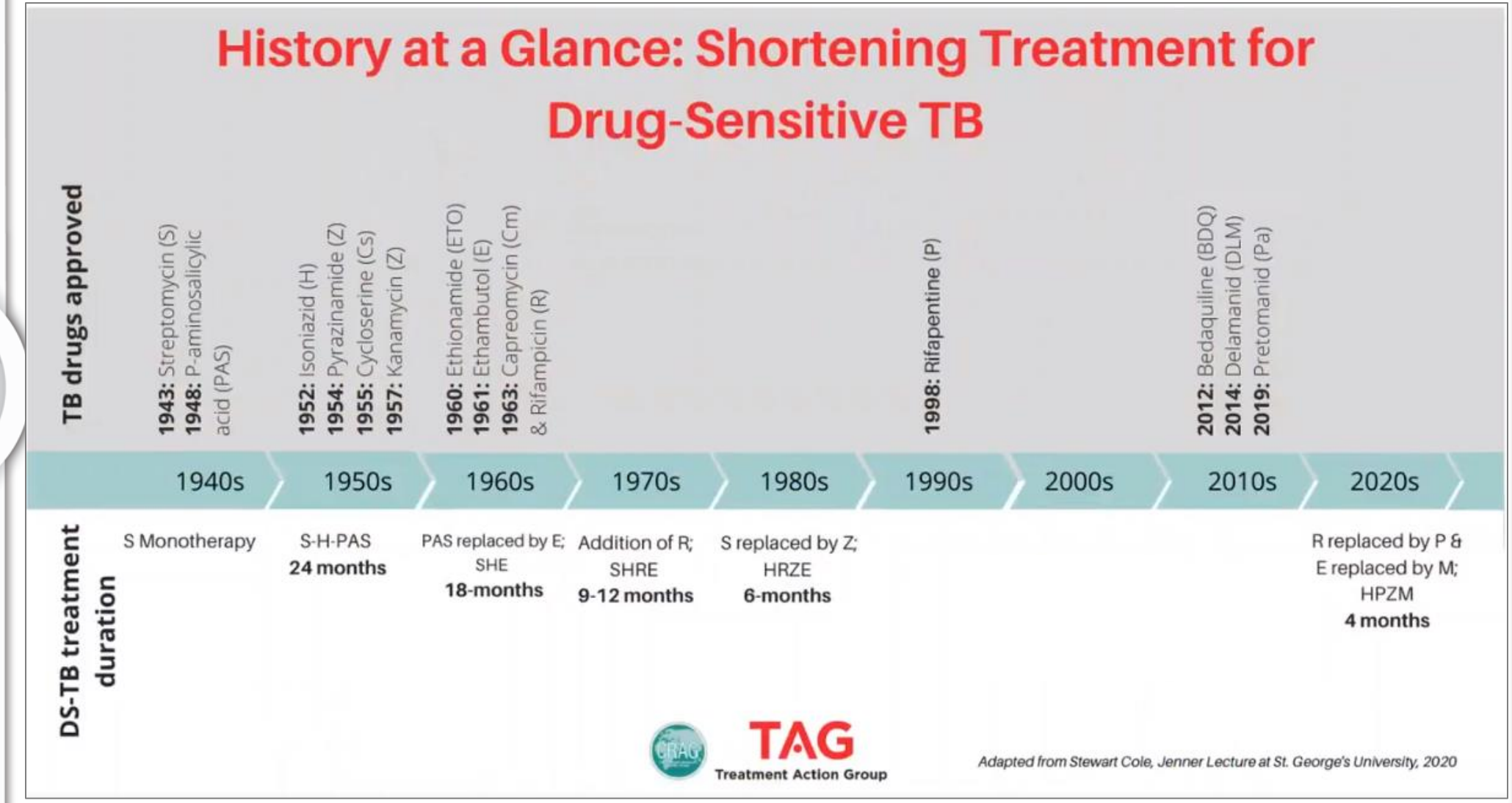
http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

Treating patients with HIV and TB

Treating TB with rifamycin antibiotics (rifabutin, rifampin, and rifapentine)	Recommended regimens may require dose adjustment. See the drug–drug interaction tables (Table 24a, Table 24b, Table 24c, Table 24d, and Table 24e) and Tuberculosis/HIV Coinfection for information on ARV use with rifamycin antibiotics.	Rifamycin antibiotics are inducers of CYP3A4 and UGT1A1 enzymes, causing significant decreases in concentrations of PIs, INSTIs, and RPV.

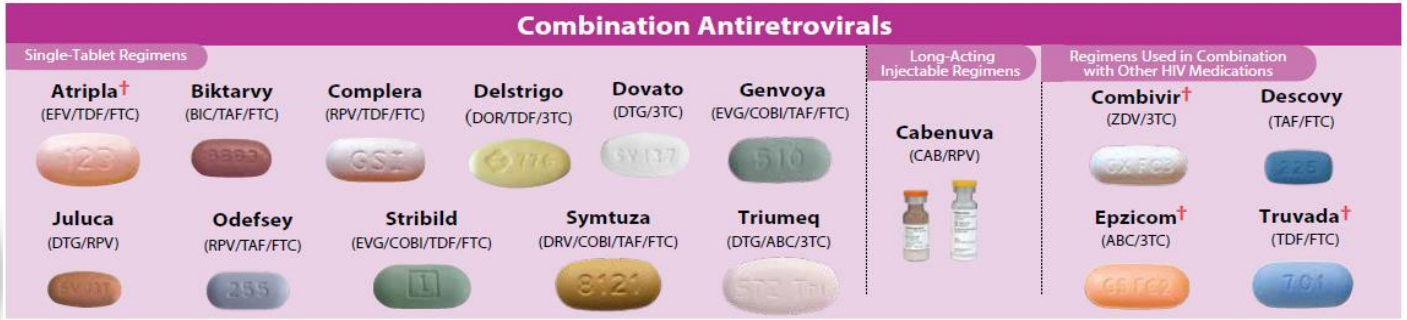
Note: INH, EMB, PZA and FQs are all safe with antiretroviral medications

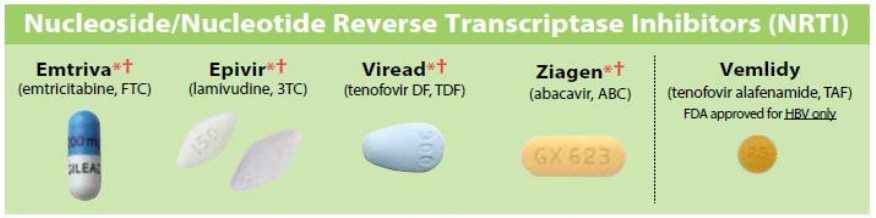
History at a Glance: Shortening Treatment for Drug-Sensitive TB

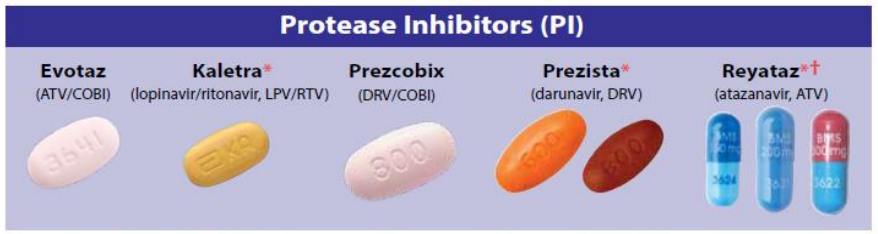


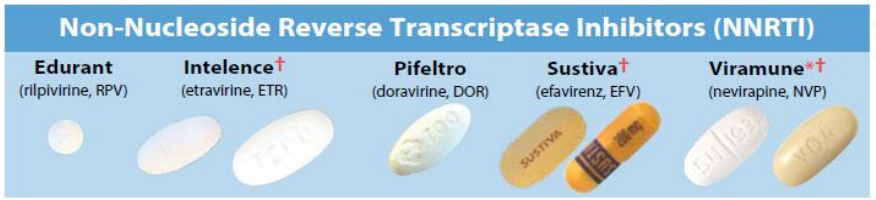
Provided by Anna Turkova

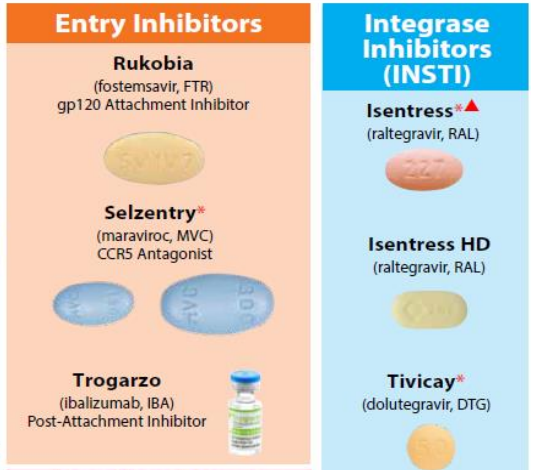
Medications for Treatment of HIV (since AZT in 1987)

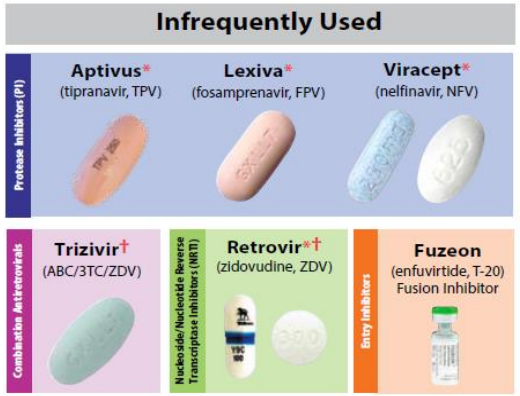


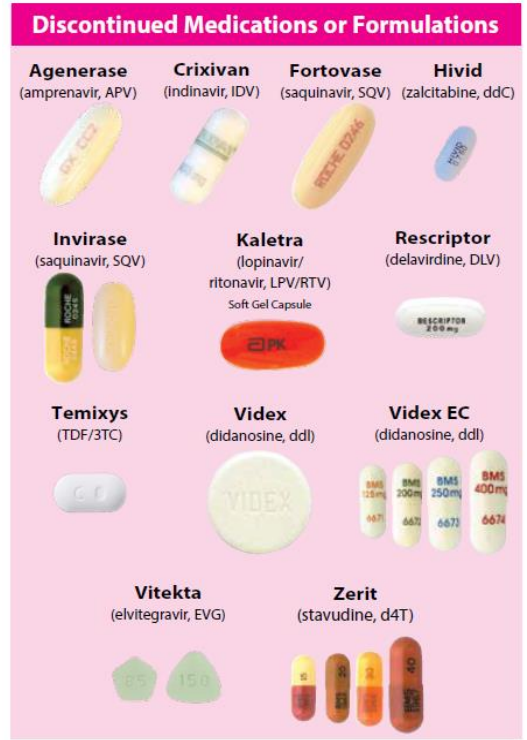


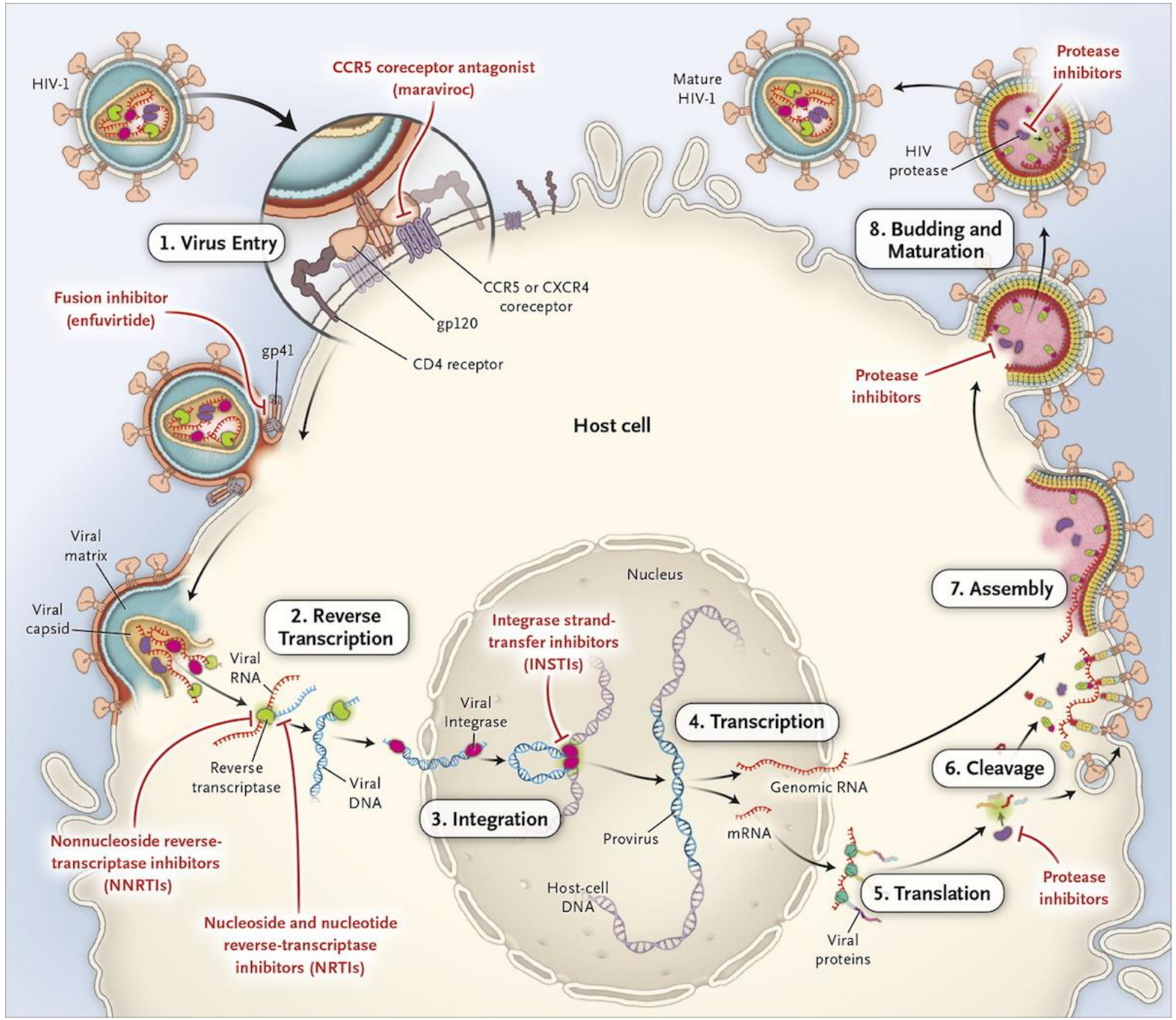


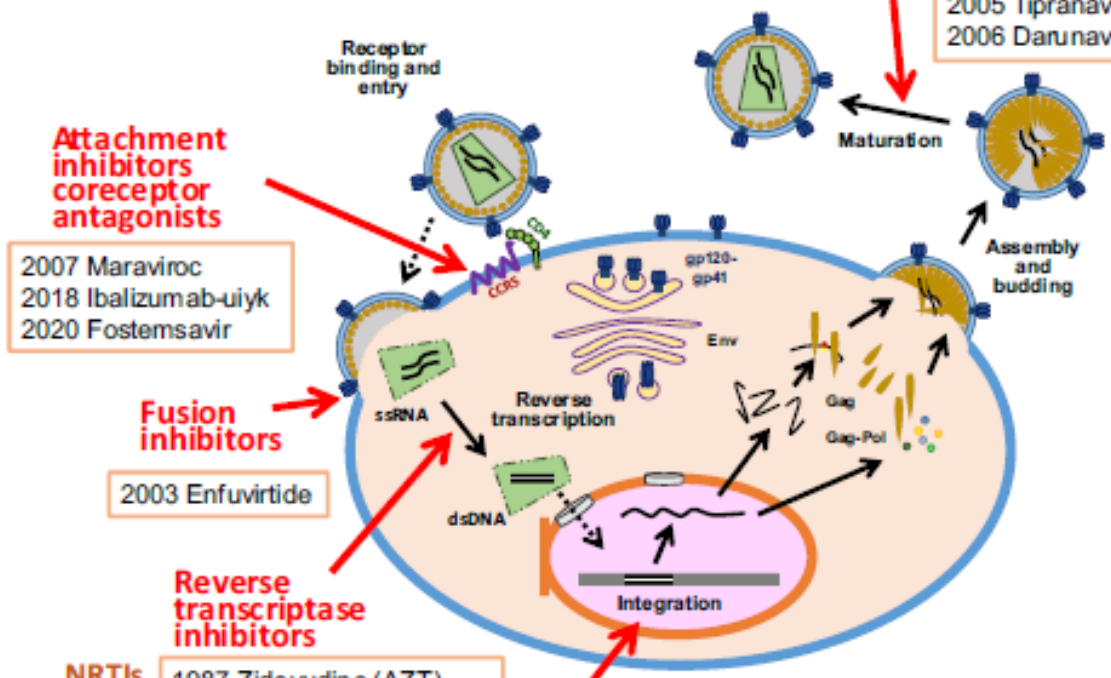









HIV-1
CCR5 coreceptor antagonist (maraviroc)
1. Virus Entry
CCR5 or CXCR4 coreceptor
gp120
CD4 receptor
Fusion inhibitor (enfuvirtide)
gp41
Host cell
Mature HIV-1
Protease inhibitors
HIV protease
8. Budding and Maturation
Protease inhibitors
Viral matrix
Viral capsid
2. Reverse Transcription
Viral RNA
Reverse transcriptase
Viral DNA
Nucleus
Integrase strand-transfer inhibitors (INSTIs)
Viral Integrase
3. Integration
4. Transcription
Provirus
Host-cell DNA
Genomic RNA
mRNA
5. Translation
Viral proteins
6. Cleavage
7. Assembly
Protease inhibitors
Nonnucleoside reverse-transcriptase inhibitors (NNRTIs)
Nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs)



Protease inhibitors

- 1995 Saquinavir
- 1996 Ritonavir
- 1996 Indinavir
- 1997 Nelfinavir
- 2000 Lopinavir (/r)
- 2003 Atazanavir (/r, /c)
- 2003 Fosamprenavir
- 2005 Tipranavir (/r)
- 2006 Darunavir (/r, /c)

Attachment inhibitors coreceptor antagonists

- 2007 Maraviroc
- 2018 Ibalizumab-uiyk
- 2020 Fostemsavir

Fusion inhibitors

- 2003 Enfuvirtide

Reverse transcriptase inhibitors

NRTIs

- 1987 Zidovudine (AZT)
- 1991 Didanosine
- 1992 Zalcitabine
- 1994 Stavudine
- 1995 Lamivudine
- 1998 Abacavir
- 2001 Tenofovir (TDF, TAF)
- 2003 Emtricitabine

NNRTIs

- 1996 Nevirapine
- 1997 Delavirdine
- 1998 Efavirenz
- 2008 Etravirine
- 2011 Rilpivirine
- 2018 Doravirine

Integrase inhibitors

- 2007 Raltegravir
- 2012 Elvitegravir (/c)
- 2013 Dolutegravir
- 2018 Bictegravir
- 2021 Cabotegravir

Antiretrovirals and Rifamycins

- Contraindicated combinations
  - Rifapentine and
    - any ARV (other than efavirenz, raltegravir or dolutegravir)
  - Rifampin and
    - Protease inhibitors
    - Doravirine, etravirine, nevirapine, rilpivirine (both PO and IM)
    - Maraviroc with a strong CYP3A inhibitor
    - EVG/cobi (TDF/FTC), bictegravir, cabotegravir (both PO and IM)
    - TAF
  - Rifabutin and
    - Etravirine with a protease inhibitor
    - Rilpivirine IM
    - EVG/cobi (TDF/FTC), bictegravir, cabotegravir IM
    - TAF

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

HIV medication and rifamycin combinations that do not require dose adjustment

- Rifampin and efavirenz (only with EFV 600 mg, not 400 mg)

- Rifabutin and
  - Etravirine (*IF* no PI involved)
  - nevirapine (use with caution)
  - Cabotegravir
  - Dolutegravir
  - Raltegravir
  - FTR (if no PI is used)

- Rifapentine and
  - Efavirenz (LTBI only)
  - Dolutegravir (LTBI only and only IF patient is virally suppressed and taking 50 mg/day of dolutegravir)
  - Raltegravir (LTBI only)

Antiretrovirals and Rifamycins

- Combinations requiring dosing adjustments
  - Rifampin and
    - Raltegravir: ↑ raltegravir to 800 mg BID
    - Dolutegravir: ↑ dolutegravir to 50 mg BID
    - Maraviroc (without a CYP3A inhibitor): MVC 600 mg twice daily
  - Rifabutin and
    - Protease inhibitors (boosted and not): ↓ rifabutin to 150 mg daily ~~or 300 mg TIW~~
    - Efavirenz: ↑ rifabutin to 450-600 mg daily or 600 mg TIW
    - Rilpivirine: ↑ RPV dose to 50 mg once daily
    - Doravirine: ↑ DOR to 100 mg twice daily
    - Maraviroc (with a CYP3A inhibitor): ↓MVC 150 mg twice daily
    - Maraviroc (without a CYP3A inhibitor): MVC 300 mg twice daily
    - FTR with PI: ↓ rifabutin to 150 mg daily

TB Drug	ARV Drugs	Daily Dose
Isoniazid	All ARVs	5 mg/kg (usual dose 300 mg)
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
Pyrazinamide	All ARVs	**Weight-based dosing** • *Weighing 40–55 kg*: 1,000 mg (18.2–25.0 mg/kg) • *Weighing 56–75 kg*: 1,500 mg (20.0–26.8 mg/kg) • *Weighing 76–90 kg*: 2,000 mg (22.2–26.3 mg/kg) • *Weighing >90 kg*: 2,000 mg[f]
Ethambutol	All ARVs	**Weight-based dosing** • *Weighing 40–55 kg*: 800 mg (14.5–20.0 mg/kg) • *Weighing 56–75 kg*: 1,200 mg (16.0–21.4 mg/kg) • *Weighing 76–90 kg*: 1,600 mg (17.8–21.1 mg/kg) • *Weighing >90 kg*: 1,600 mg[f]

https://clinicalinfo.hiv.gov/en/guidelines

PLWH with MDR - Bedaquiline

- Use with Protease Inhibitors……no
- Use with Efavirenz/etravirine……no
- Nevirapine, doravirine, rilpivirine, no change in dose of either medication
- TAF, INSTIs, CCR5 inhibitors, no clue…….

IRIS
(Immune Reconstitution Inflammatory Syndrome)

Restoration of pathogen-specific immune responses to opportunistic infections

- Unmasking IRIS
  - New presentation of a previously subclinical infection
- Paradoxical IRIS
  - Deterioration of a treated infection
  - Reported in 8-40% of patients starting ART after TB diagnosis
  - Most occur within 3 months of starting ART
  - Predictors:
    - CD4 count < 50
    - Higher on-ART CD4 count
    - High pre-ART and lower on-ART viral load
    - Severity of disease (high pathogen burden)
    - < 30 days between start of TB and HIV treatments

Tuberculosis/HIV Coinfection | NIH

IRIS
(Immune Reconstitution Inflammatory Syndrome)

- Rule out other causes
  - Drug resistance (do you have susceptibilities?)
  - Other opportunistic infections
- Management
  - Mild cases use NSAIDS
  - More severe cases use steroids

Treatment - Summary

- TB testing for PLWH remains inadequate in many circumstances
- Every effort should be made to treat within the CDC guidelines to
  - increase the chances of treatment success,
  - decrease the chances of relapse and
  - minimize the length of time with toxicities.
- Rifamycins are the cornerstone of treatment for TB. Though drug interactions with ARVs are a concern, data continues to emerge regarding effective dosing options.
- HIV infection does not negatively impact patients with TB disease if diagnosed early and treated appropriately

Thank you for your attention

Questions?

Lisa.Armitige@dshs.texas.gov

1-800-TEX-LUNG

www.HeartlandNTBC.org