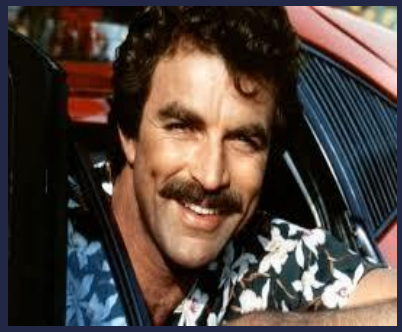
HIV and Tuberculosis in Saskatchewan

Dr Kris Stewart
TB Control and Prevention
September 12, 2015

Overview

- Brief review of history of tuberculosis
- Review of TB microbiology, transmission, diagnosis and treatment
- Social, pathological and therapeutic interaction of HIV and TB
- Review epidemiology of HIV and TB globally, nationally and in Saskatchewan
- Unique challenges and approaches to delivering care for HIV TB coinfection in Saskatchewan
  - Case presentation



Microbiology of TB

Mycobacterium tuberculosis complex

- a small, aerobic, non motile bacillus
- divides every 16 to 20 hours
- grows only intra-cellularly

Transmission

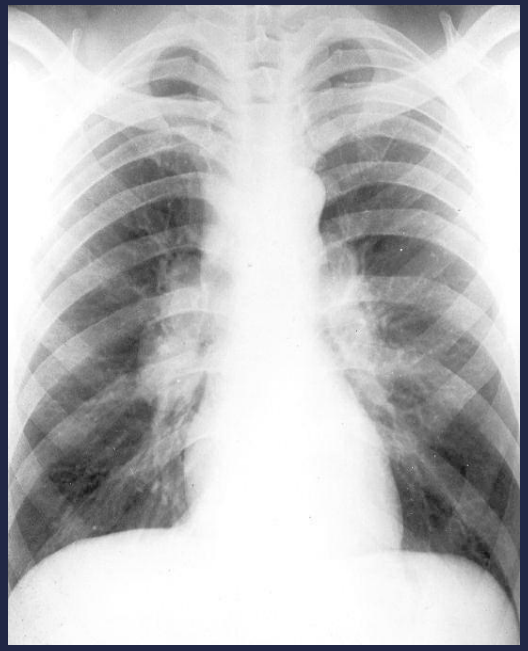
- Aerosolized particles
  - Sneeze = 40 000 mycobacteria
  - Infectious dose ~ 10 mycobacteria
- Pulmonary and Laryngeal Infections only
- Transmission from children less likely as no forceful cough.
- Risk of transmission increased by
  - Crowded spaces with poor ventilation
  - 10 hrs in close quarters

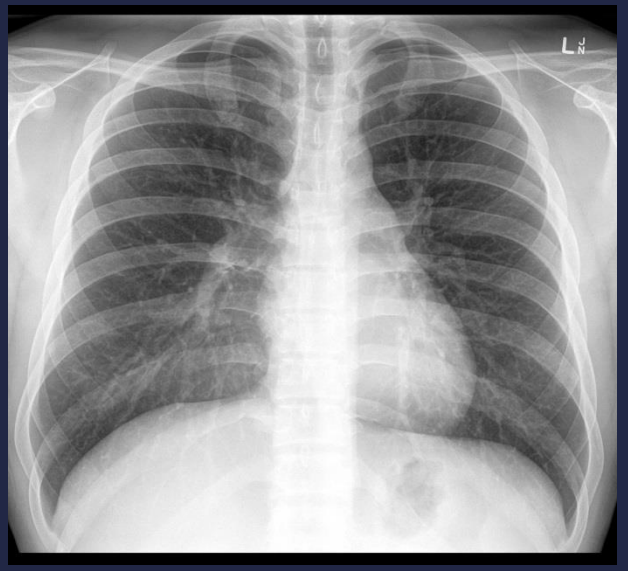
Pathogenesis of TB

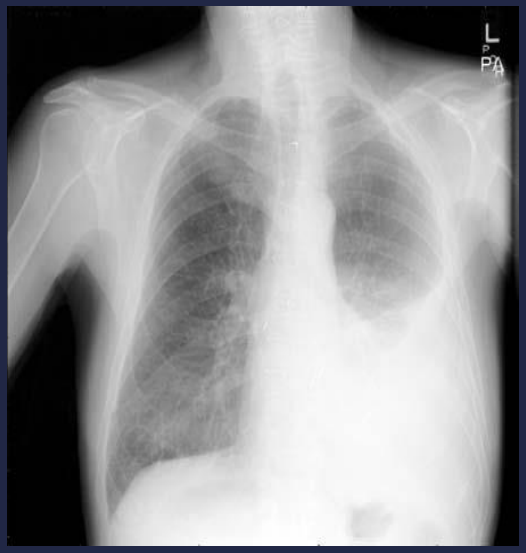
- Inhaled into airspace ‘non specific’ immune cells (alveolar macrophages) and form a collection of bacilli and immune cells (Ghon focus).
- Infection with mycobacteria tuberculosis results in stimulation of ‘specific’ immune cells (lymphocytes)
- Prominent role of CD4 T cell lymphocytes.
- These lymphocytes are critical in preventing this small collection from opening up and letting TB spread throughout lung causing infectious TB.

Pathogenesis of TB

- If initial infection is not contained through activation of immune system, then primary disease occurs.
- After initial infection primary disease occurs in about 5% of adults but much more likely in those under 5 years old, especially infants.
  - Pulmonary
  - Pleural
  - Lymphatic
  - Disseminated



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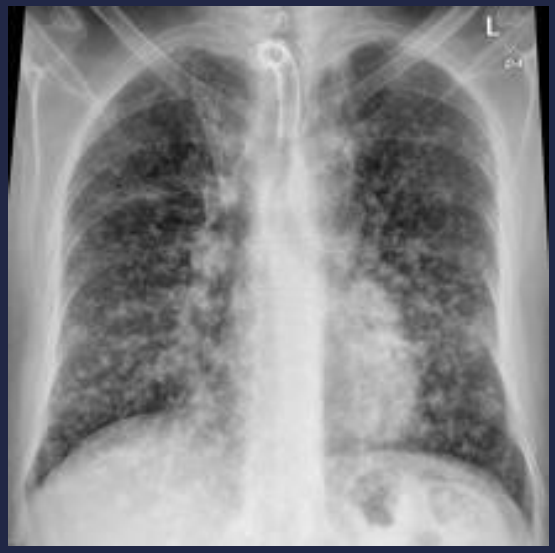
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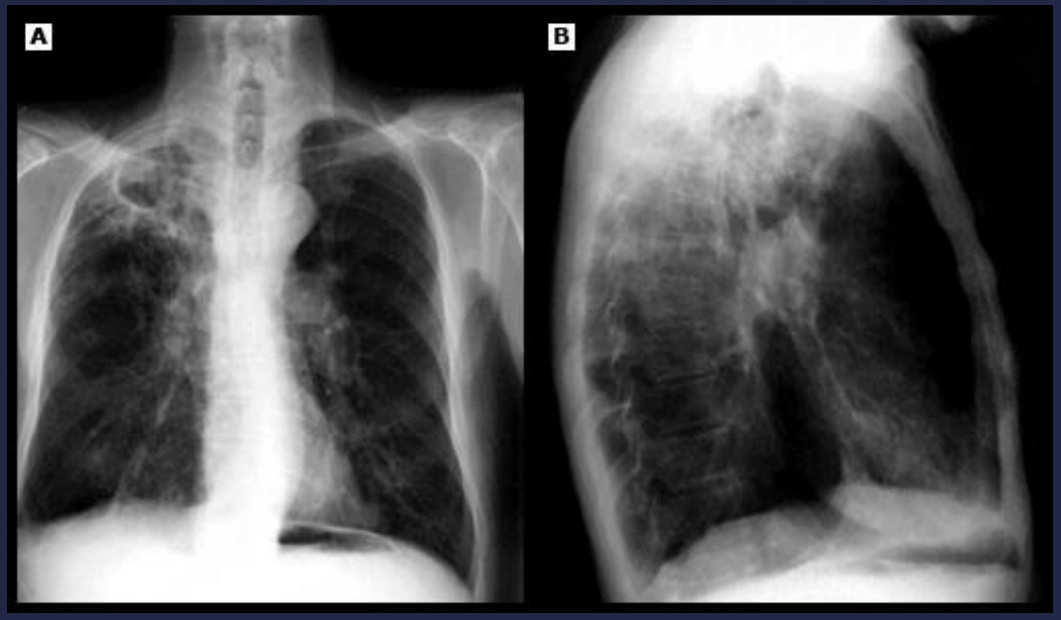
Pathogenesis of TB

- If early infection is successfully contained, bacilli ‘go to sleep’ and latent TB develops
- Latent state maintained by immune system.
- Reactivation occurs if immune system cannot maintain latent state.
    - 5% chance for the rest of their life
- Reactivation TB usually manifests as upper lobe parenchymal disease, sometimes with cavitation.


A
B

Pathogenesis of TB

- 5% develop primary disease within 2 years of infection.
- Those who do not develop primary infection will about a 5% lifetime risk of developing reactivation TB
- Therefore there is about a 10% lifetime risk of active disease
- 90% will never develop active disease
- This 10% risk is much higher if person has other medical conditions which affect the immune systems ability to maintain the latent state.

Risk Factors for Development of Active TB among persons Infected

Risk Factor	Estimated Risk of TB Relative to Persons with No Known Risk Factor
AIDS	110 – 170
HIV	10 – 110
Transplantation	20 – 74
Leukemia, lymphoma	1 - 35
Chronic renal failure with hemodialysis	1.6 – 25
Recent TB infection (< 2 years)	15
Abnormal CXR (FN disease)	6 – 19
Steroid therapy	4.9
Diabetes	2 – 4.1
Young age when infected (0 – 4 years)	2 – 5
Cigarette smoker	2 – 3
Refugees	2

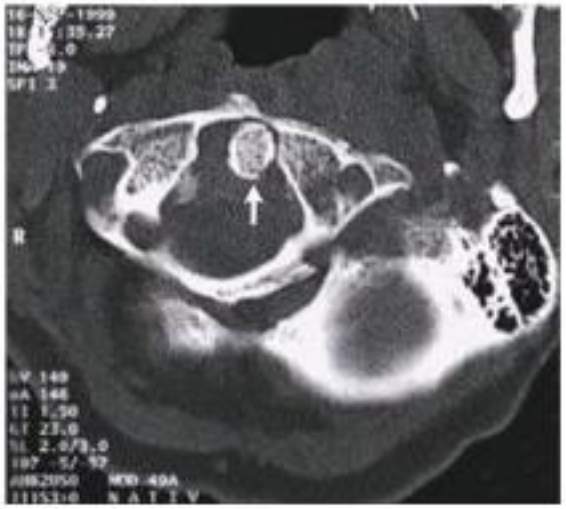
Source: Canadian TB Standards, 2007 and Greenway et al. CMAJ 2011

Clinical Manifestations

- 90% pulmonary

- 15 to 20% extra pulmonary (outside of the lungs)
  - More common in immunocompromised, including HIV
    - Skin (tuberculomas)
    - CNS (Tb meningitis and brain and spine abscess)
    - Genitourinary (mass in kidney and hematuria)

    - Can develop at any site
      - Joints, mouth, eyes, abdominal wall



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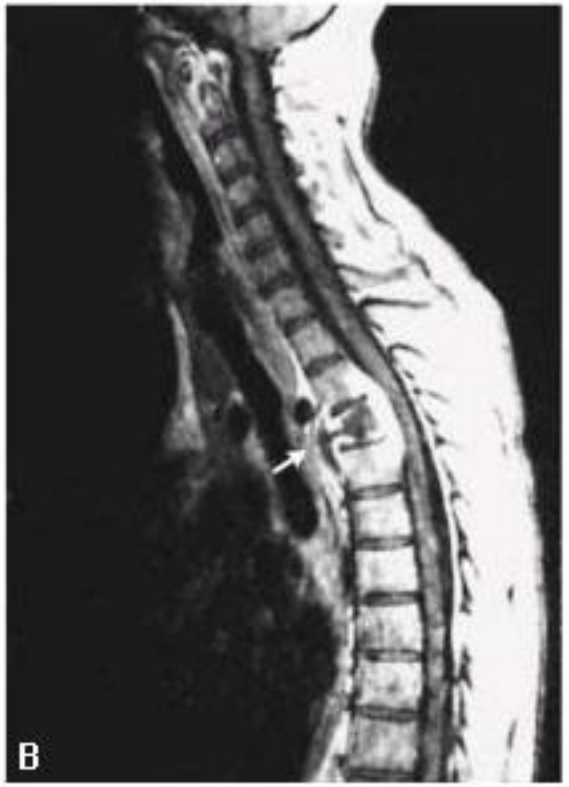

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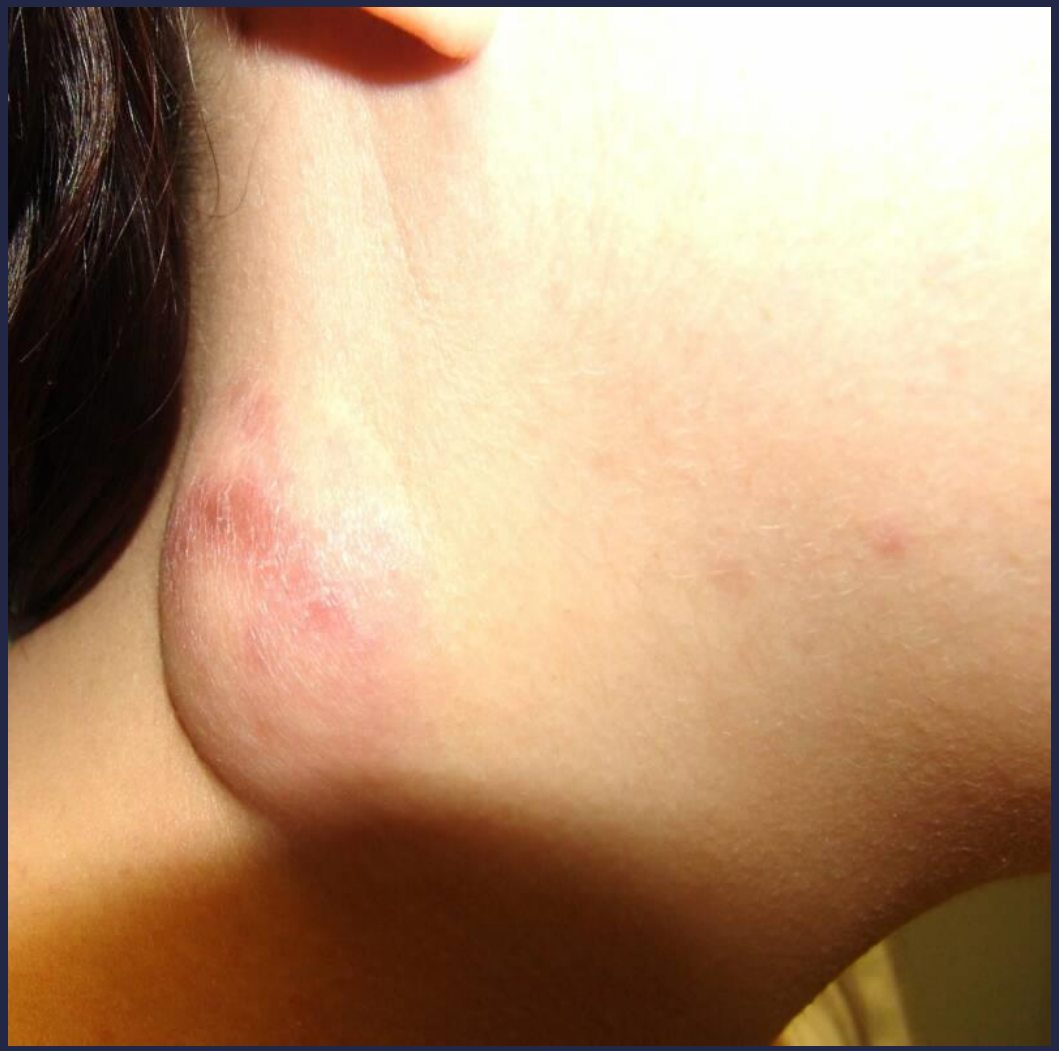


Clinical Manifestations

- Non resolving cough
  - Usually productive, less often dry, hemoptysis is uncommon
- Unexplained weight loss
  - Over weeks to months
- Night Sweats
  - Several times per week, drenching
- Extrapulmonary disease
  - Back pain, neurologic deficits, hematuria, swollen mass

Diagnosis of Latent Tuberculosis

- Tuberculin Skin Testing
  - Aka 'Mantoux'
  - False positives and negatives

- IGRA (interferon gamma release assay)
  - One step procedure
  - Better specificity
  - More expensive
  - Available in SK October 1st
    - Prince Albert, Saskatoon, Regina

Diagnosis of Active TB

- Clinical
  - Pretest probability
  - Clinical history
- Radiology
  - CXR is first line study
  - Also CT Scan MRI and Ultrasound

Diagnosis of Active TB

- Microbiology
  - Sputum or other (pleural fluid, urine, aspiration)
    - Smear (1 to 3 days)
      - Sample examined with microscope for AFB
    - Gene Xpert (3 hours to 2 days)
      - Sample probed for TB genetic material
    - Culture and Sensitivity (4 to 8 weeks)
      - Sample grown in TB specific media in petri dish


Acid-fast bacilli
8


GeneXpert
USAID
Cepheid
USAID / Flickr

Infectiousness suggested by hierarchy of testing

- Smear + ve are most infectious
- Smear - ve, Gene Xpert +ve next most infectious.
- Smear -ve, Xpert -ve, culture +ve are least infectious but still potentially infectious.

Isolation

- Need for isolation determined by smear and Xpert.
  - If Xpert negative, no isolation required
    - but could later be found to be culture positive = conundrum!
    - So, we would still have to do a contact tracing on someone we said didn't need isolation = oops!

Isolation

- When to stop isolation determined by combination of smear status, duration of treatment and clinical improvement
  - Xpert not helpful here
  - Different criteria for home versus institutional setting

Prognosis of active TB

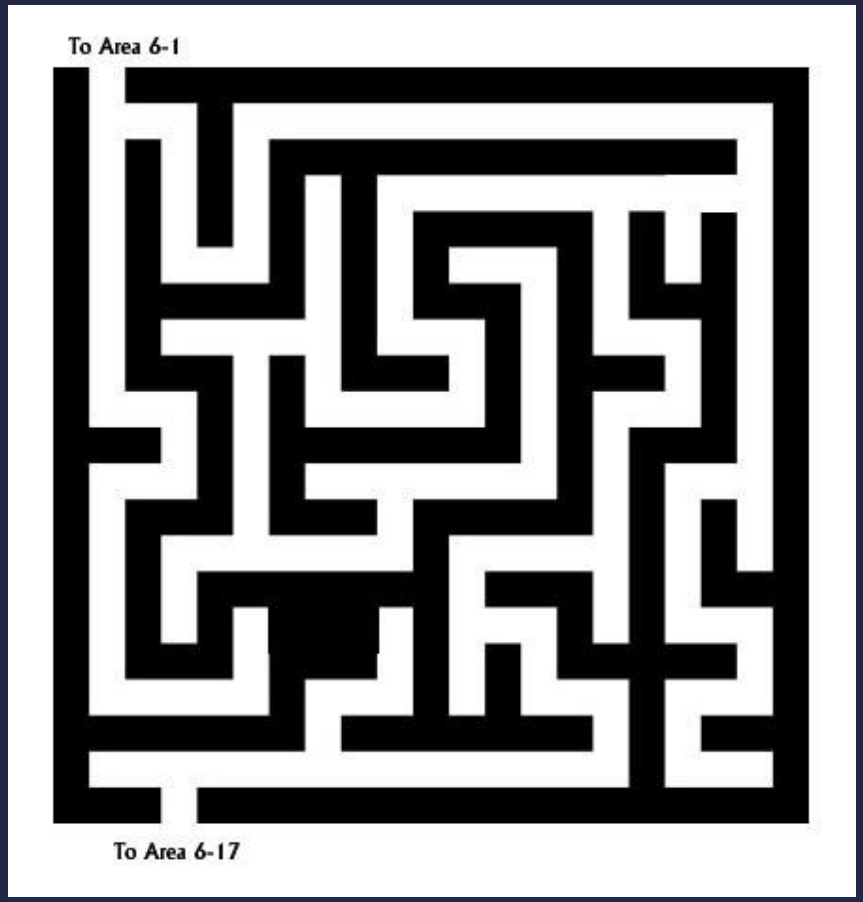
- Untreated
  - Greater than 50% mortality
- Treatment effective unless
  - late presentation
  - drug resistance
  - comorbidities
  - malabsorption
  - Immunosuppression
- In SK, nearly all TB related deaths are in HIV infected patients
- Often, addiction and late presentation is also a factor.

Treatment

- Main 4 drugs:
  - Isoniazid (INH), Rifampin, Ethambutol, Pyrazinamide
    - Abbreviated as IREZ
- Main 2 drugs
  - Isoniazid, Rifampin
- When we are worried about resistance or patients cant take main drugs:
  - Fluoroquinolones (levofloxacin)
  - others for MDR, XDR

Treatment

- Active regimen (always DOT)
  - 2 months intensive phase (daily or 5 x per week)
  - 4 months continuation phase (3 x per week)
  - Longer in some cases (cavity, slow response, in CNS)
- Prophylactic regimen (usually DOP)
  - INH + RMP 2 x weekly x 4 months
  - RMP daily x 4 months
  - INH daily x 9 months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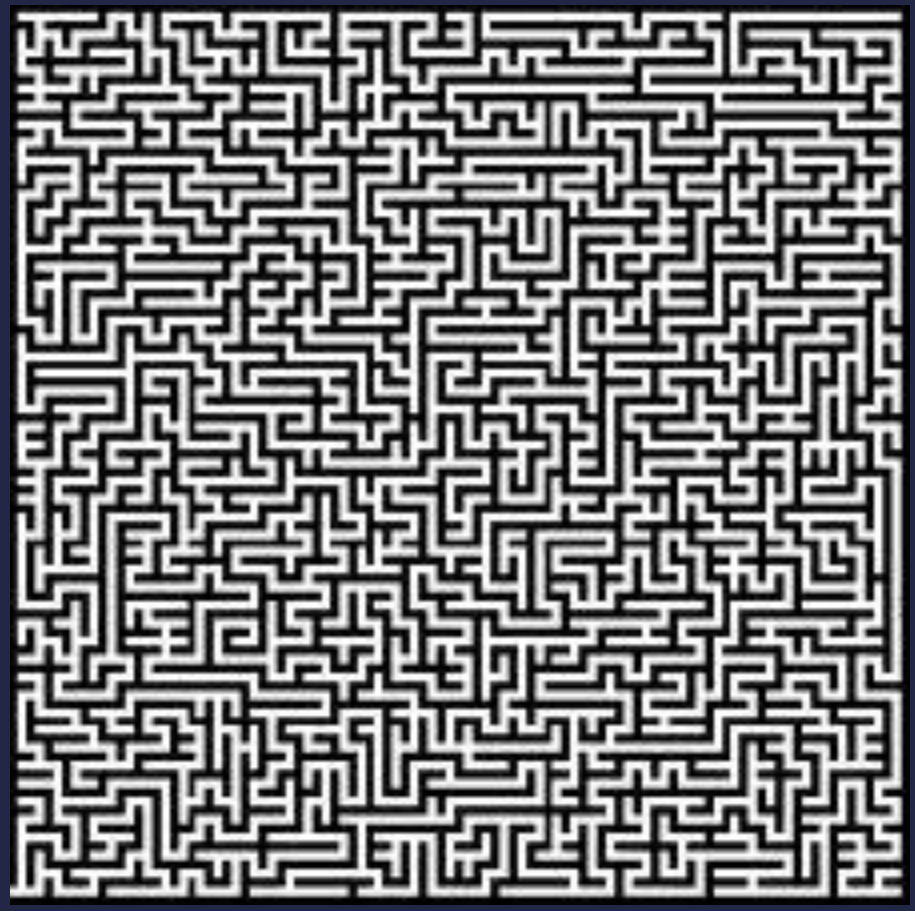


Common Scenario in Saskatchewan

- Individual from northern community presents with pneumonia, cough and wasting
  - Referred to hospital and thru X Ray and sputum analysis diagnosed with active disease
  - Treatment begun in hospital and continued at home
    - ‘non-infectious’ after 14 days of effective therapy
    - patient completes TB treatment course thru DOT and is cured.

Common scenario in Saskatchewan

- Contact Tracing is initiated at time of diagnosis.
  - Smear + 90 days
  - Smear -, culture + 30 days
- Contacts are screened for symptoms and CXR
  - Primary disease is treated as active
- The rest are screened for LTBI with TST
  - Those with + TST are offered prophylaxis or surveillance

Who gets proph?

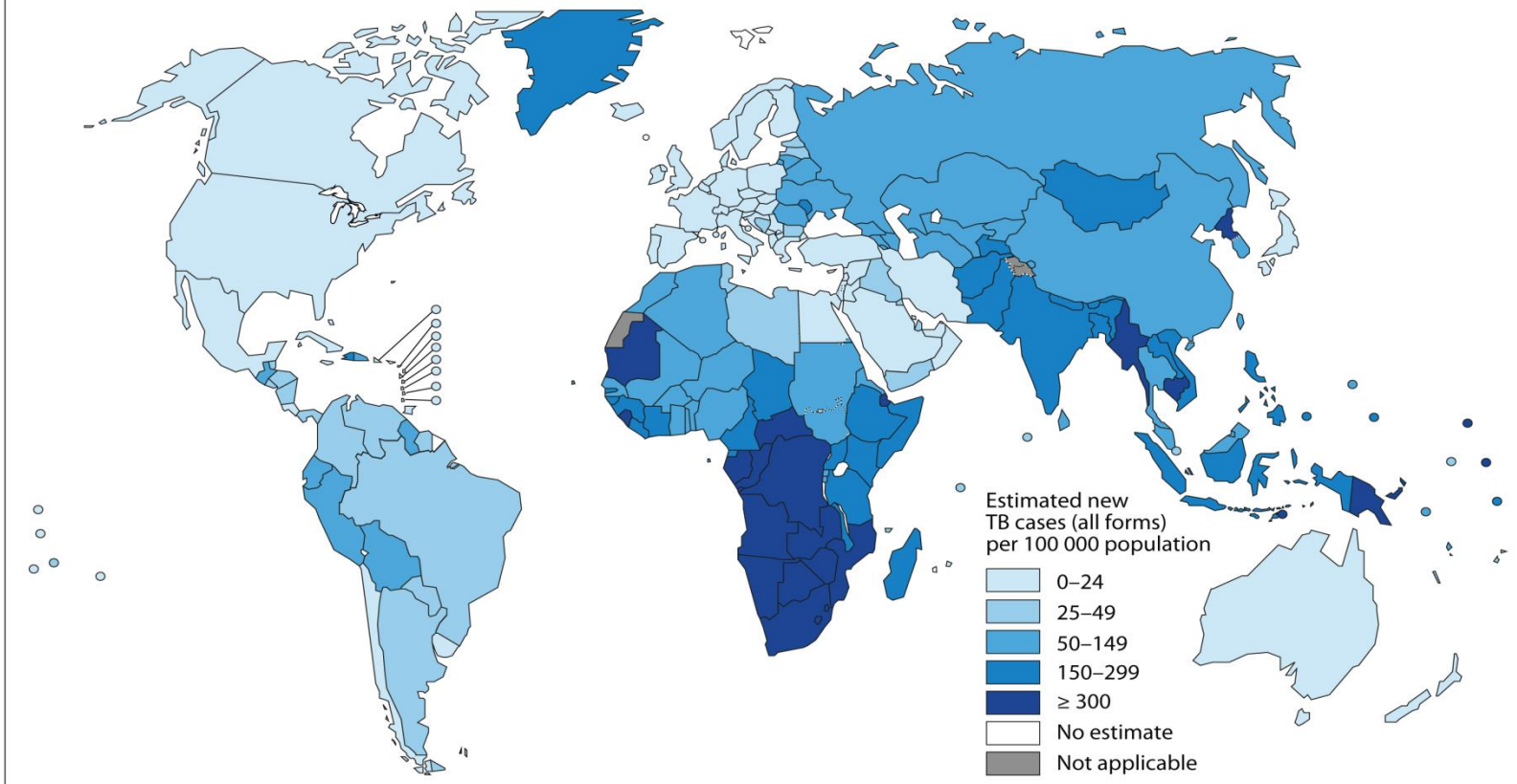
- http://tstin3d.com/

Epidemiology of TB

- Presently 1/3 of planet has latent TB (LTBI)

- Active TB
  - In 2013
    - 9 million new active cases of TB (13% coinfected with HIV)
    - 1.5 million deaths from TB
  - Millennium Development Goal (UN 2000) is to reverse TB epidemic
    - Incidence began falling in 2011
  - Between 2000 and 2013
    - 37 million lives were saved by screening for and treating TB

Estimated tuberculosis (TB) incidence rates, 2011



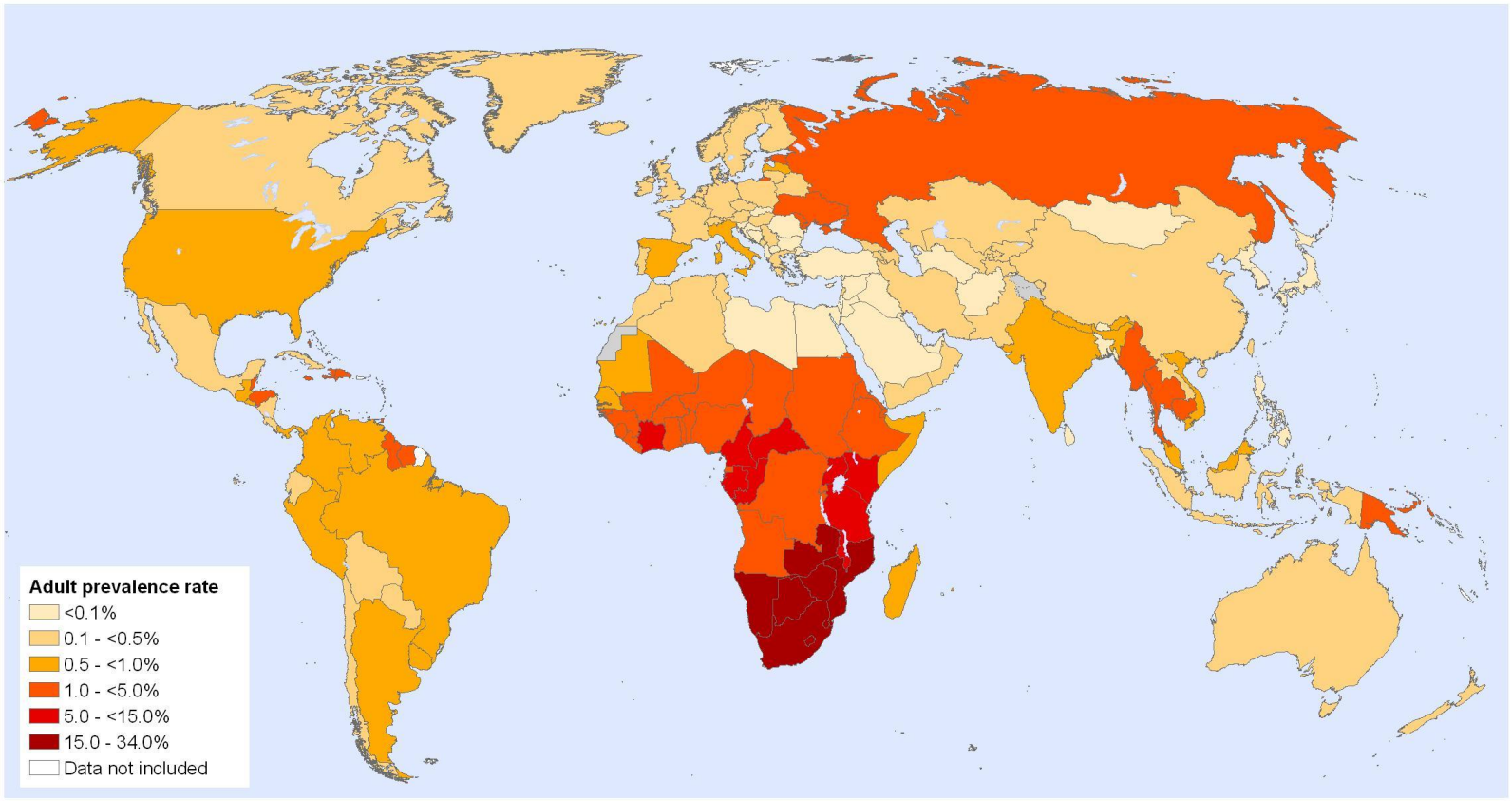
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Source: *Global Tuberculosis Report 2012*. WHO, 2012.

World Health Organization

A global view of HIV infection

39.5 million people [34.1-47.1] living with HIV in 2006



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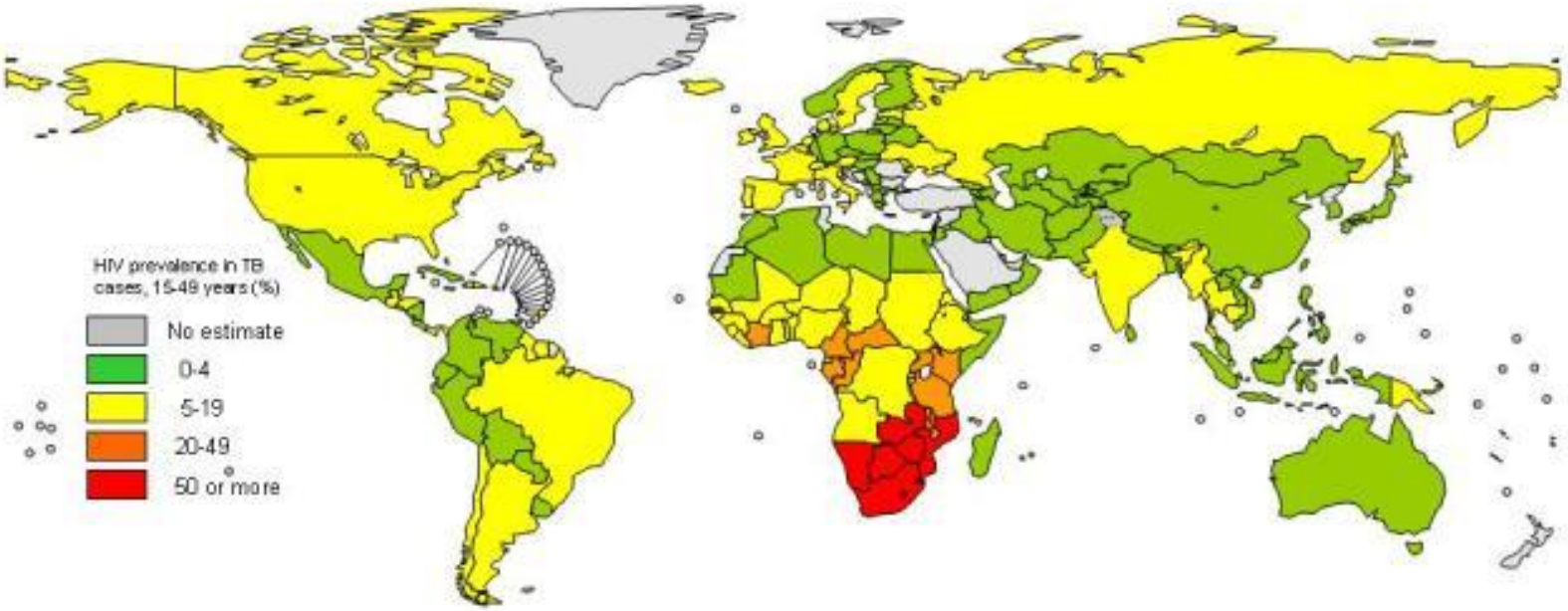
Data Source: WHO / UNAIDS
Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS)
World Health Organization

World Health Organization

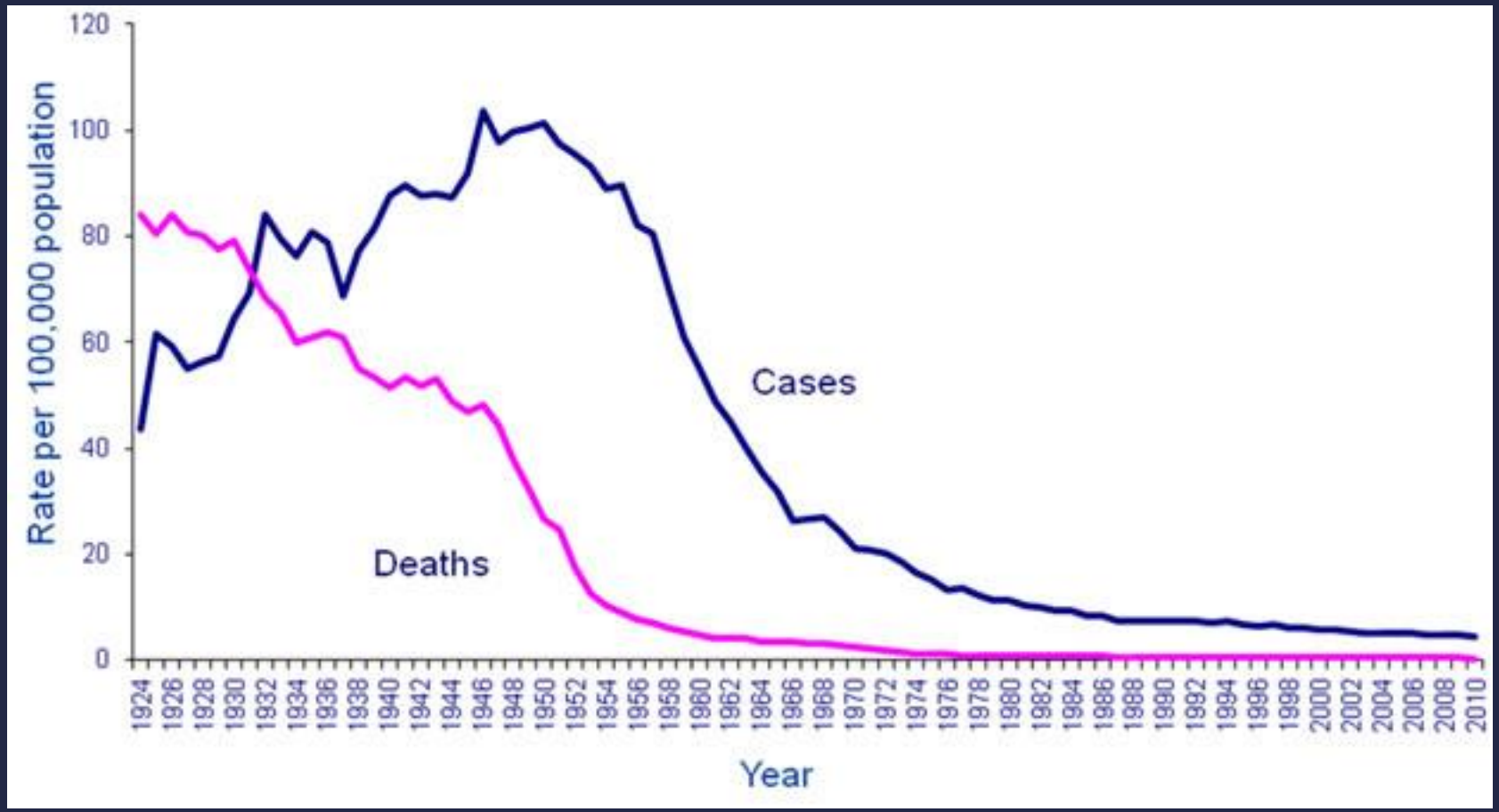
Estimated HIV prevalence in new TB cases, 2005



Epidemiology of TB in Canada

- 2012 there were 1686 new or retreated cases of active TB
  - Incidence of 4.8 / 100 000 nationally
  - Incidence of 234 / 100 000 in Nunavut
  - Incidence of 8.5 /100 000 in Saskatchewan

TB in Canada


Rate per 100,000 population
120
100
80
60
40
20
0
Cases
Deaths
1924
1926
1928
1930
1932
1934
1936
1938
1940
1942
1944
1946
1948
1950
1952
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1956
1958
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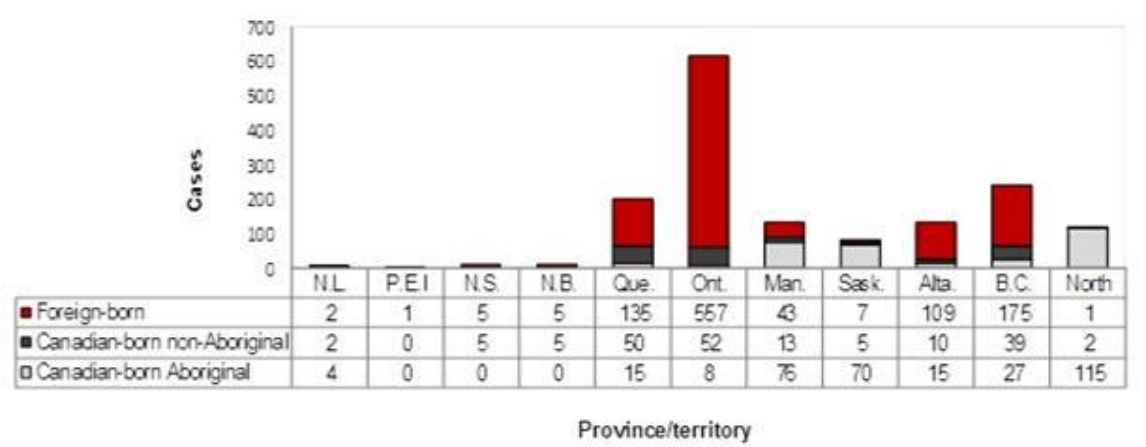
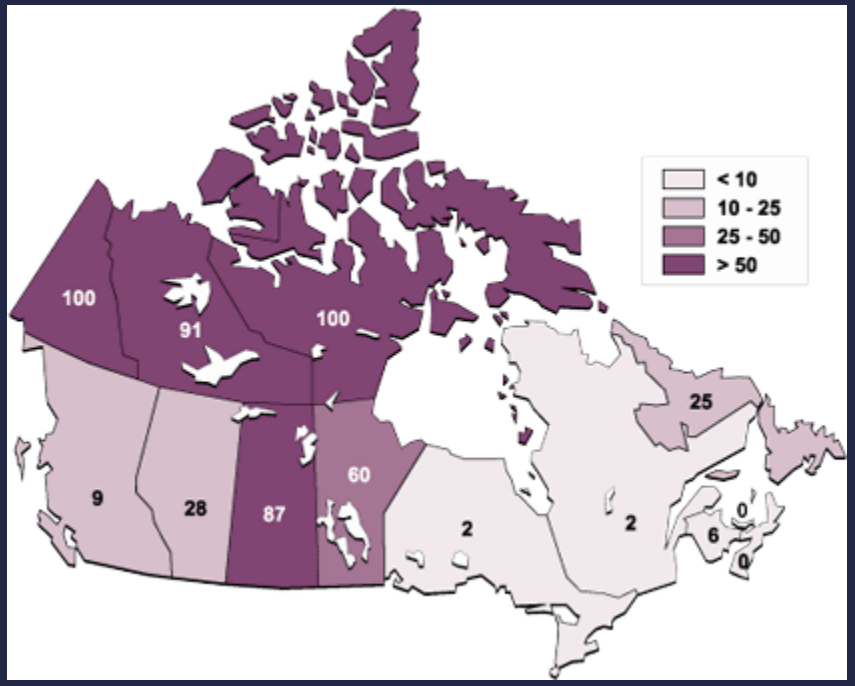
2008
2010
Year

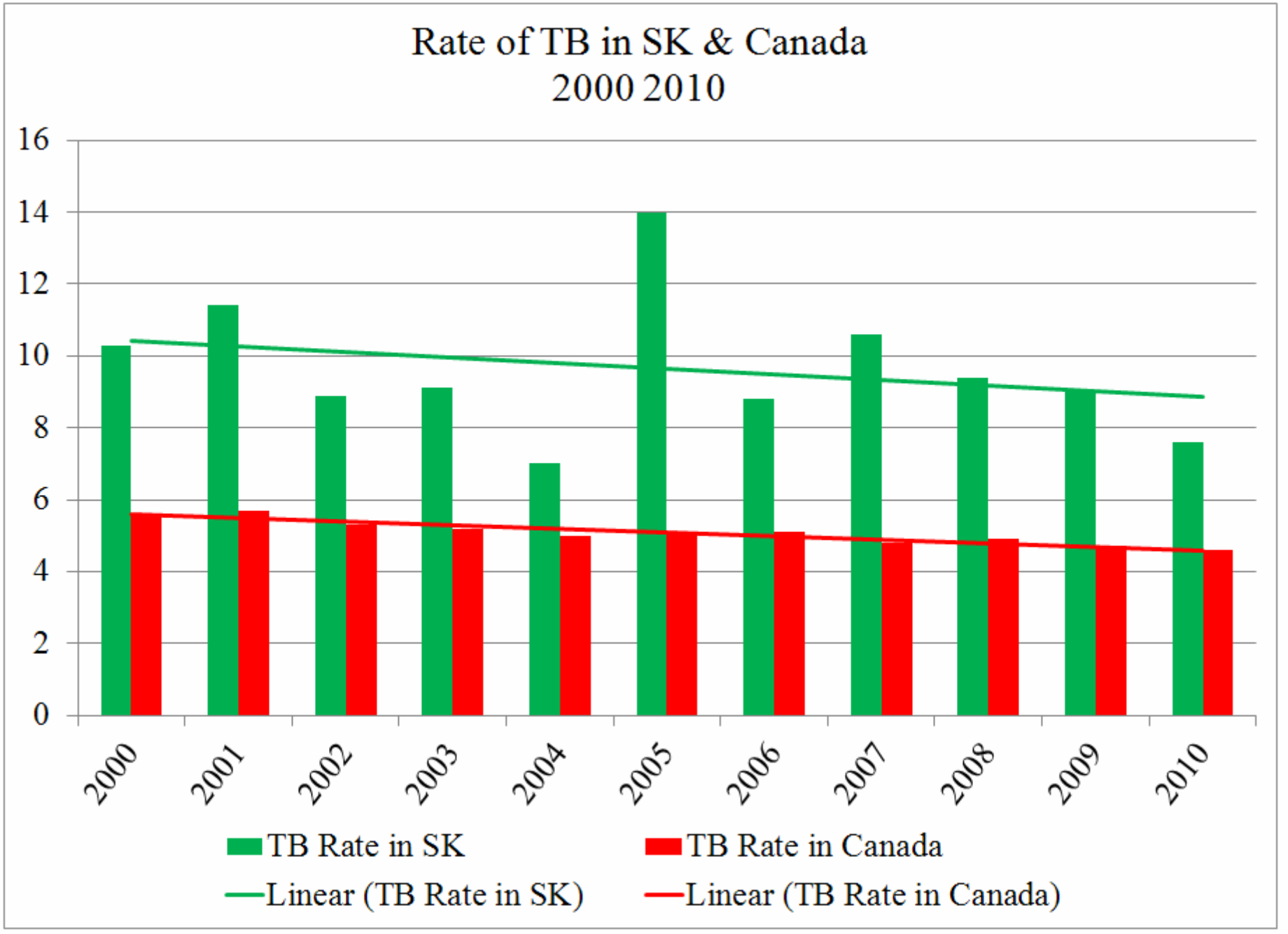
TB in Saskatchewan

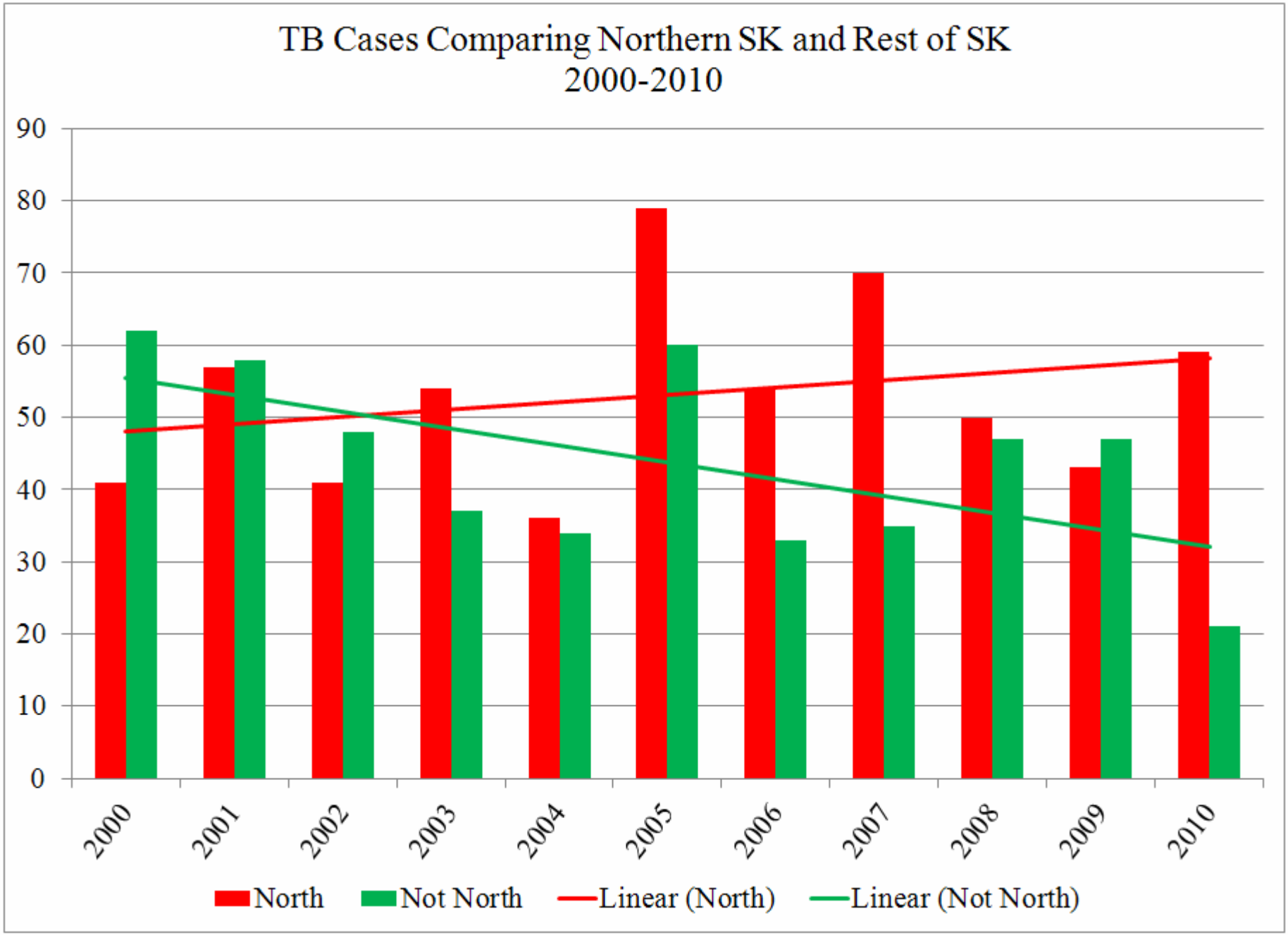


	N.L.	P.E.I	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.	North
Foreign-born	2	1	5	5	135	557	43	7	109	175	1
Canadian-born non-Aboriginal	2	0	5	5	50	52	13	5	10	39	2
Canadian-born Aboriginal	4	0	0	0	15	8	76	70	15	27	115

Relative proportion of cases of TB in aboriginals by Province

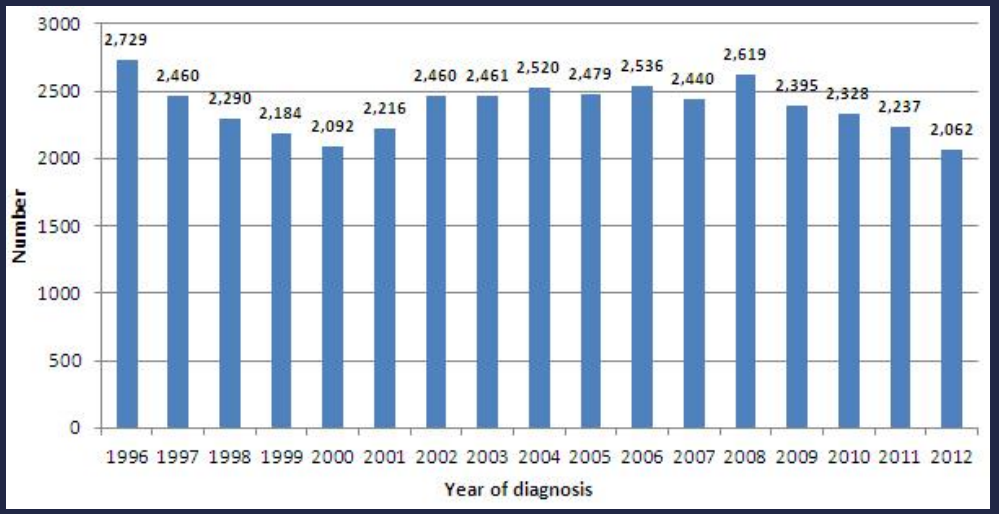



Rate of TB in SK & Canada
2000 2010
16
14
12
10
8
6
4
2
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
TB Rate in SK
TB Rate in Canada
Linear (TB Rate in SK)
Linear (TB Rate in Canada)


TB Cases Comparing Northern SK and Rest of SK
2000-2010
90
80
70
60
50
40
30
20
10
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
North
Not North
Linear (North)
Linear (Not North)

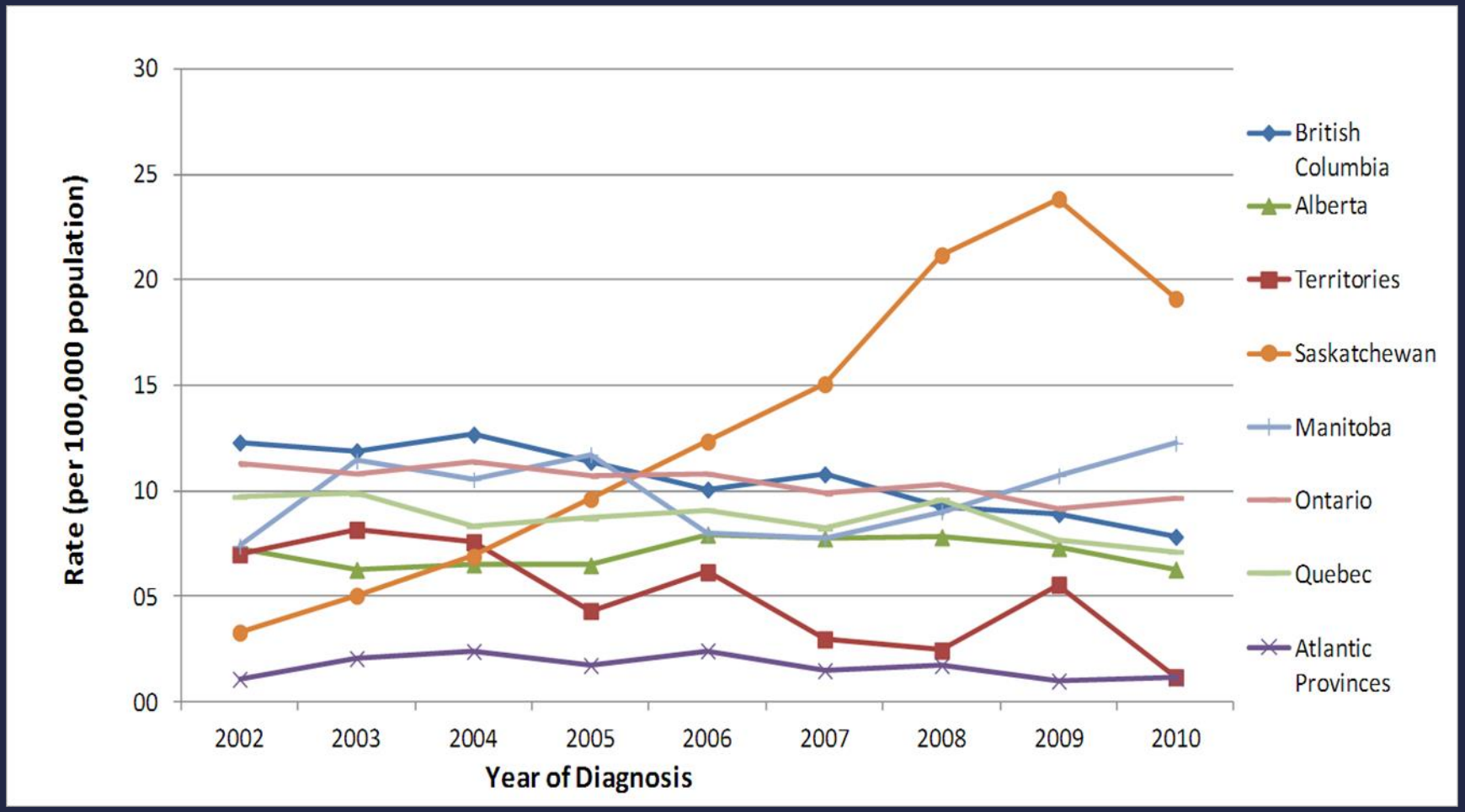
HIV in Canada by Risk Category

- In 2013 estimated
  - 78 511 living with HIV
  - 2 090 new infections
    - Drop by 0.4% from 2012
    - Lowest ever



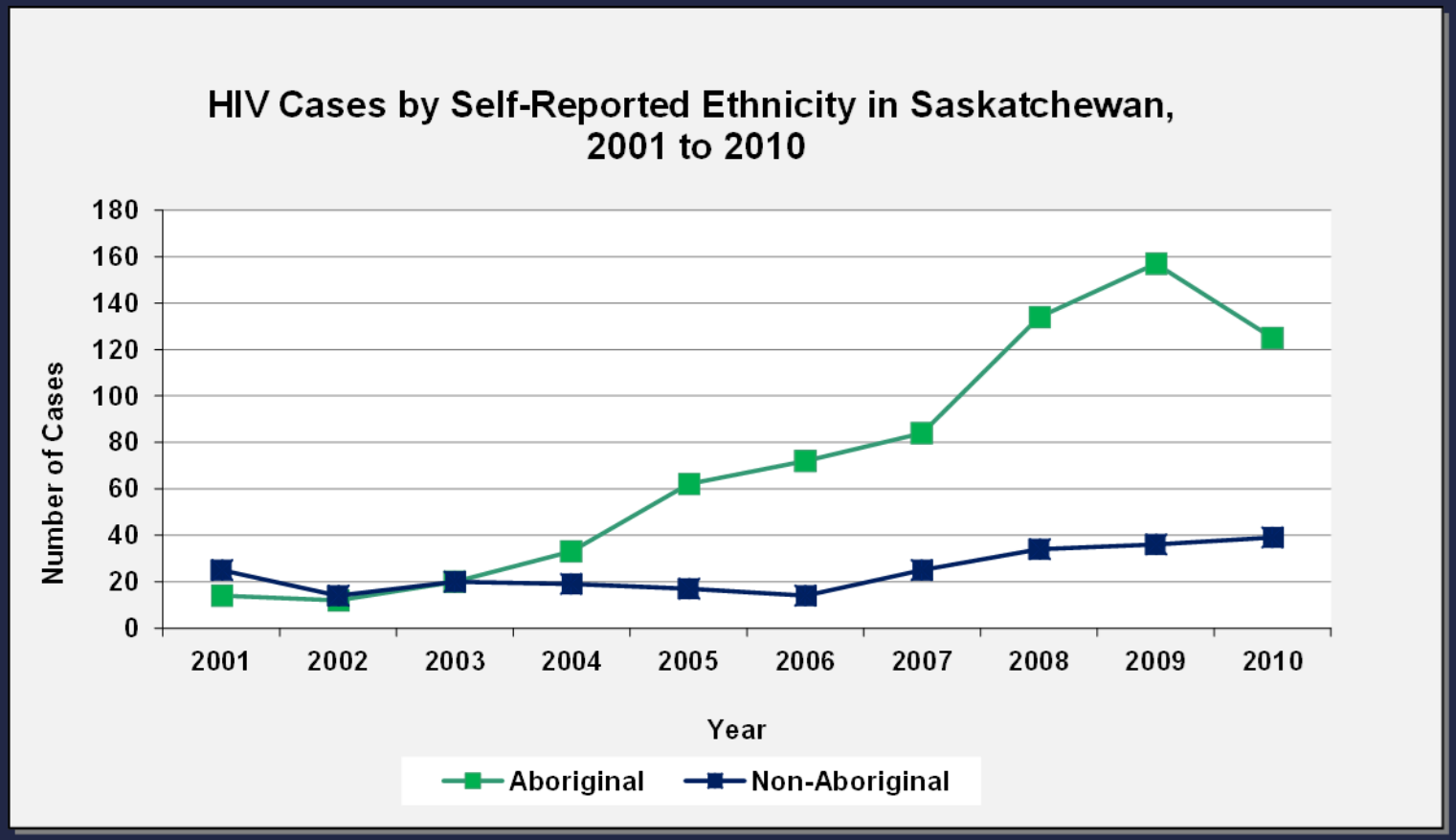
- Public Health Agency of Canada
- www.publichealth.gc.ca

HIV in SK by Province and Year




National rate: 5.9 per 100,000
Yukon
2.7
Northwest Territories
2.3
Nunavut
0.0
British Columbia
5.9
Alberta
6.5
Manitoba
9.2
Saskatchewan
11.4
Ontario
6.1
Quebec
5.6
Newfoundland and Labrador
1.3
Prince Edward Island and Nova Scotia
1.7
New Brunswick
0.8

HIV in Saskatchewan by Ethnicity and Year

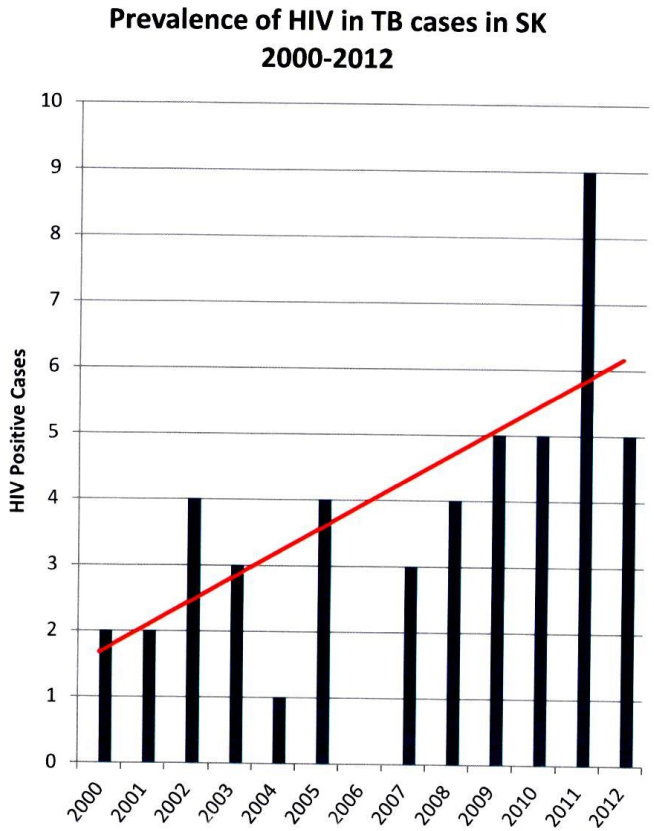


Social interaction of HIV and TB

- Both infections disproportionately affect
  - First Nations
  - Foreign born Canadians
  - Incarcerated individuals
  - Illicit Drug Users

- More likely to have either/ both/ all of
  - Low income
  - Insecure housing
  - Food insecurity

HIV and active TB in Saskatchewan



Year	TB	HIV (N)	HIV (%)
2000	103	2	1.9%
2001	115	2	1.7%
2002	89	4	4.5%
2003	91	3	3.3%
2004	70	1	1.4%
2005	139	4	2.9%
2006	87		0.00%
2007	105	3	2.9%
2008	97	4	4.1%
2009	90	4	4.4%
2010	81	5	6.2%
2011	83	9	10.8%
2012	89	5	5.6%
Total	1239	47	3.8%

TB in HIV positive patient

- Untreated HIV leads to decreasing and impaired CD4 T cells.
- In those who are HIV + but with CD4 count > 200, TB occurs in a similar fashion to those without HIV but still at a significantly higher rate.
- Having an undetectable viral load from ARV will decrease this risk but still not to the baseline risk.

TB in HIV positive patient

- All HIV patients are more likely to develop primary disease because unable to contain initial infection and induce latency.

- In those with CD4 counts of less than 200 cells/mm3
    - Rapidly progressing, quickly fatal, disseminated infection of TB.
        - Milliary TB

TB in HIV positive patient

- In those with latent TB, loss of the specific immune cell (CD4 lymphocyte) control of the ‘sleeping TB cellular collection (Ghon focus) and the reawakening of the TB and spread into surrounding lung tissue or elsewhere.

TB in HIV positive patient

- CD4 counts of less than 200 cells/mm^3
  - Reactivation
    - Atypical CXR abnormalities more likely
    - Extra pulmonary TB more likely
      - Extra thoracic LN, pleural, renal, and skeletal, CNS
    - More difficult to diagnose, lack of symptoms.
      - CT chest and abdomen, LN aspiration
      - Induced and bronchoscopy sputum collection
      - Urine cultures for TB

TB in HIV positive patient

- Those with latent TB and AIDS can develop active disease at a rate of 10% per year.
- Compared to a 10% lifetime risk for non HIV.

Risk Factors for Development of Active TB among persons Infected

Risk Factor	Estimated Risk of TB Relative to Persons with No Known Risk Factor
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Young age when infected (0 – 4 years)	2 – 5
Cigarette smoker	2 – 3
Refugees	2

Source: Canadian TB Standards, 2007 and Greenway et al. CMAJ 2011

Treatment of Active TB in those with HIV

- If not on ARV, initiate TB treatment prior to ARVs.
  - N Engl J Med. 2011;365(16):1492.

    - If CD4 < 50 and sick, start ARV 2 weeks after TB treatment

    - If CD4>50 but still features of advanced AIDS, start within 4 weeks

    - If CD4>50 and no features of advanced AIDS may start in 8 to 12 weeks

Choice of TB therapy

- Usual TB meds and regimens are effective
  - IREZ daily x 2 months, IR 3 x weekly x 4 months
  - 9 months total for cavitary disease, Potts disease, disseminated, not on ARVs
- Use of Rifampin complicates ARV use.
  - No significant drug interactions with NRTI's
  - Drug Interactions with NNRTIs, PIs, Raltegravir, Dolutegravir, Cobicistat and Maraviroc

Choice of TB therapy

- Rifabutin may be used with NRTIs, NNRTIs and PI's
  - As effective as rifampin in active disease
  - No evidence for its use in prophylaxis
  - Must dose adjust rifabutin for reverse DI's
  - Expensive
    - 6x the cost of RMP

TB treatment in HIV

- Always supplement INH with Pyridoxine
  - Decreases incidence of peripheral neuropathy

- In Saskatchewan we offer DOT to everyone and DOP in almost everyone.

Screening for LTBI in HIV

- Everyone HIV positive should receive TST or IGRA soon after diagnosis and
  - Repeat annual if living in a moderate to high risk area.

- Interpretation

  - Any TST of 5 or greater = positive

  - CD4 > 200 and TST < 5 = negative

  - CD4 < 200 and TST < 5 = inconclusive, repeat when CD4> 200.

Management of LTBI in HIV

- If considered to have + TST then should receive prophylaxis to eliminate risk of active disease

- If HIV + and a contact to an active case of TB then should be given prophylaxis independent of TST result or CD4 count or treatment status.

Prophylactic regimens for LTBI in those with HIV

- INH 300 mg po daily x 9 months
  - Best evidence
  - Tough to offer DOT
- INH and RMP twice weekly X 4 months
  - Okay for DOT
  - Rifampin involved in DI's with NNRTIs and PIs

Prophylactic regimens for LTBI in those with HIV

- INH 900 mg po 3 x weekly x 9 months, DOT
  - Forgiving of a missed dose/wk
  - Need to check liver enzymes monthly
  - If good adherence can drop down to 2 x weekly.

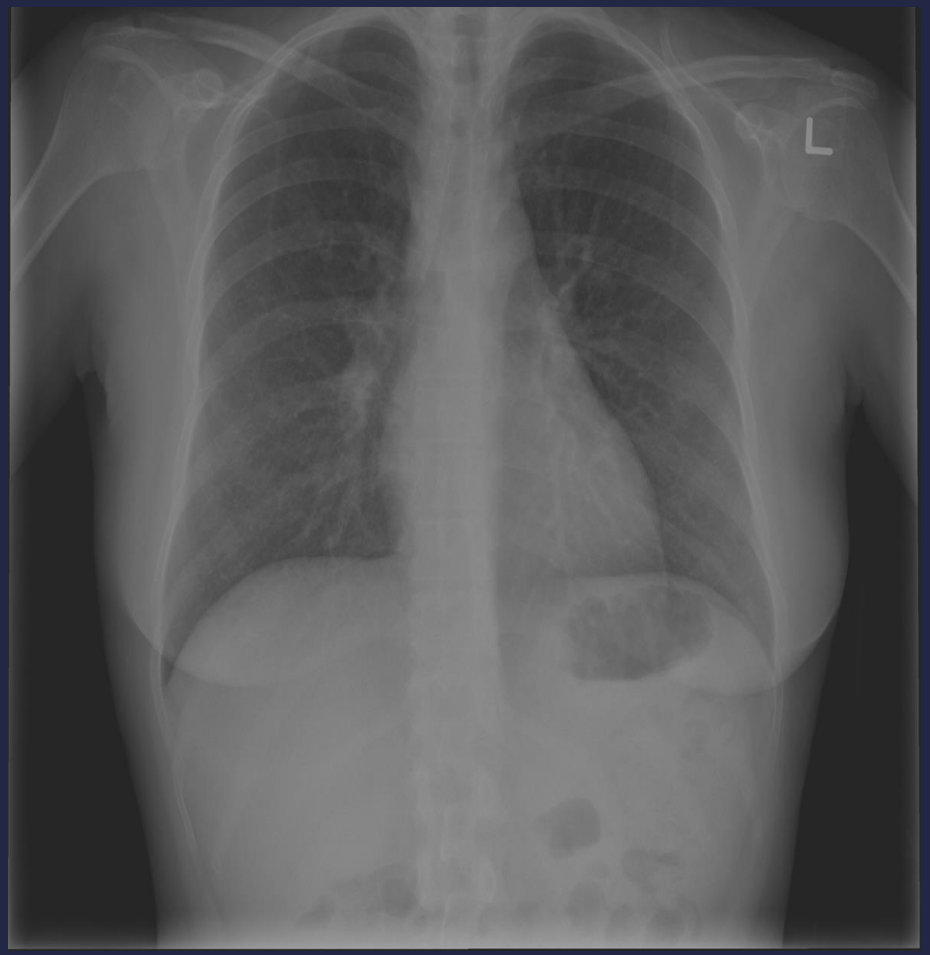
- Adapted from
  - 7th Ed Canadian Tuberculosis Standards, Chapter 6, p 12
    - » Randomized trial of INH vs. Rif + PZA for prevention of tuberculosis in HIV-1 infection Lancet March 14, 1998
  - CDC Recommendations for treatment of LTBI in HIV
    - » http://www.cdc.gov/tb/publications/ltbi/pdf/TargetedLTBI.pdf

Case 1: Sylvia

- Seen at SPH ER with cough x 1 week.

- HIV positive, treatment naïve, CD4 100
  - Not on OI prophylaxis

- On exam
  - T 38 C HR 84 BP 110/60 Sat 94% RA
  - Chest fine crackles throughout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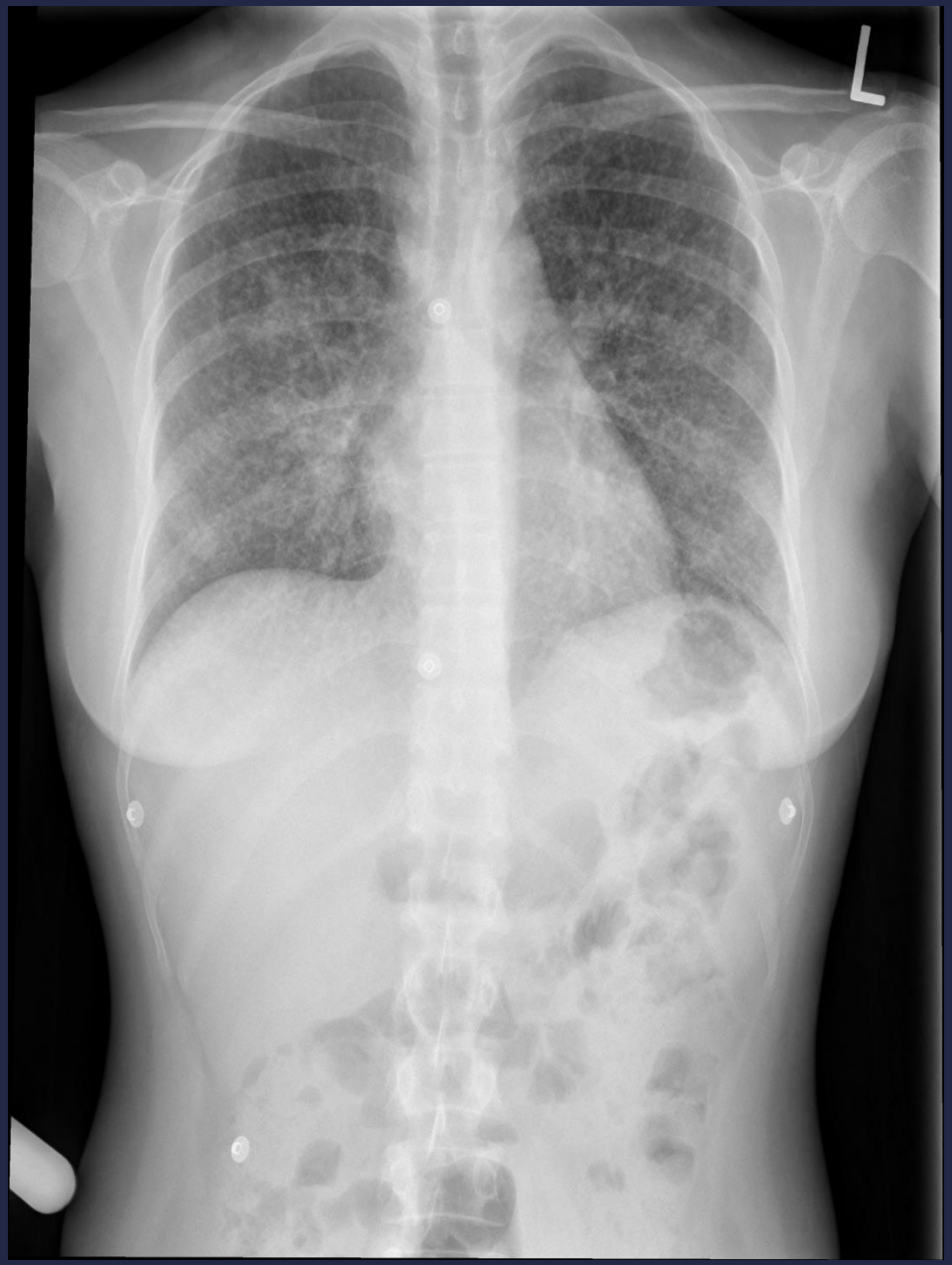
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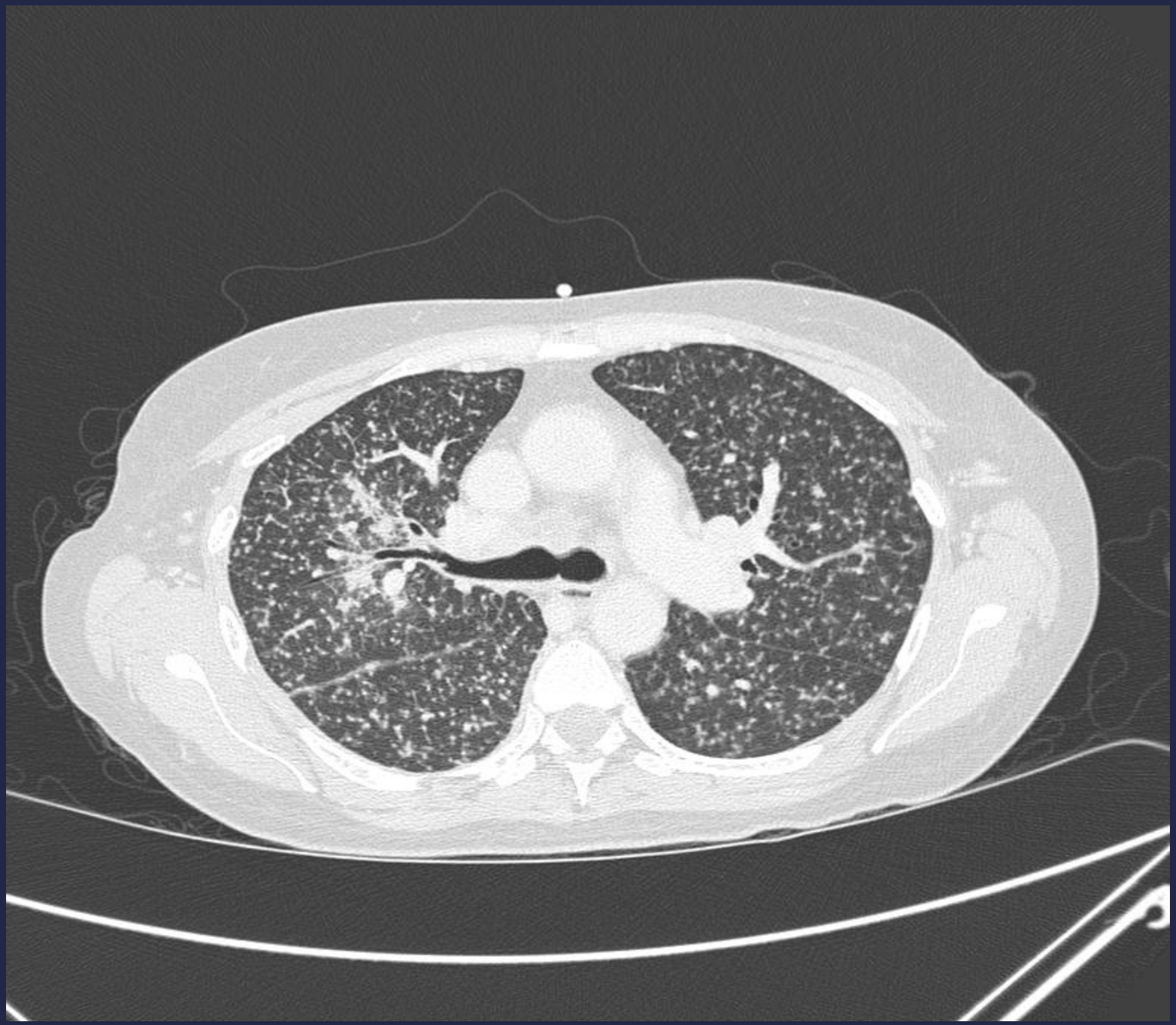


Bacteriology and Empiric Treatment

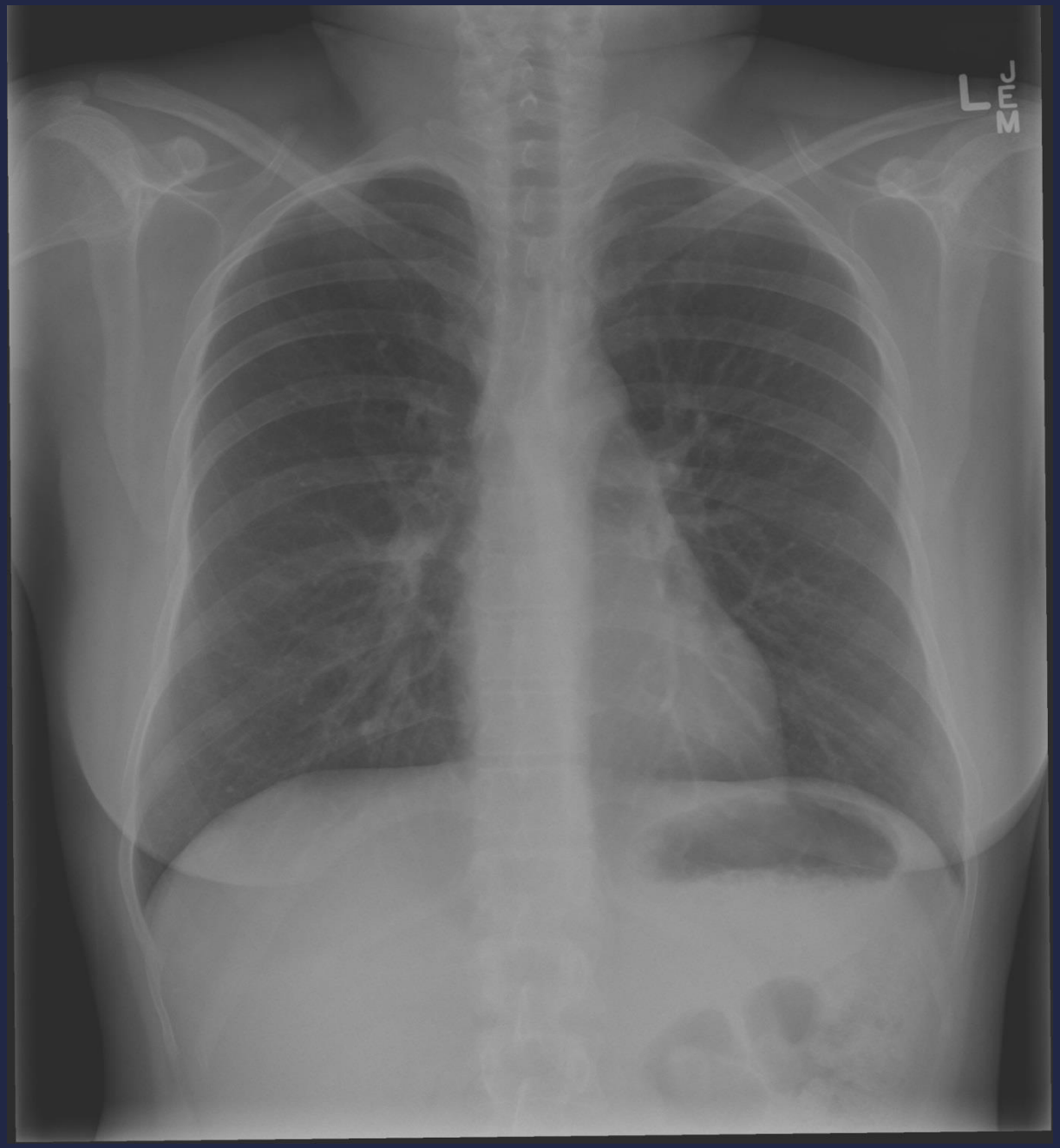
- Sputa: 1 of 3 samples 2+ smear positive AFB

- Started 4 drug regimen, daily pending culture and sensitivity results

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol

Follow up Culture and Sensitivity

- Sputum: 1 of 3 culture positive with fully sensitive *Mycobacterium tuberculosis*
- Urine: culture positive with same
- Therefore:
  - Treatment simplified to INH RMP daily for 1 month then three times weekly for eight months
- Completed TB therapy with 78% compliance
  - Likely adequate.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JEM

Need to treat HIV

- Did not show up for appointment with HIV team for 6 months
- When seen
  - CD4 count was 34, thrush, weight loss

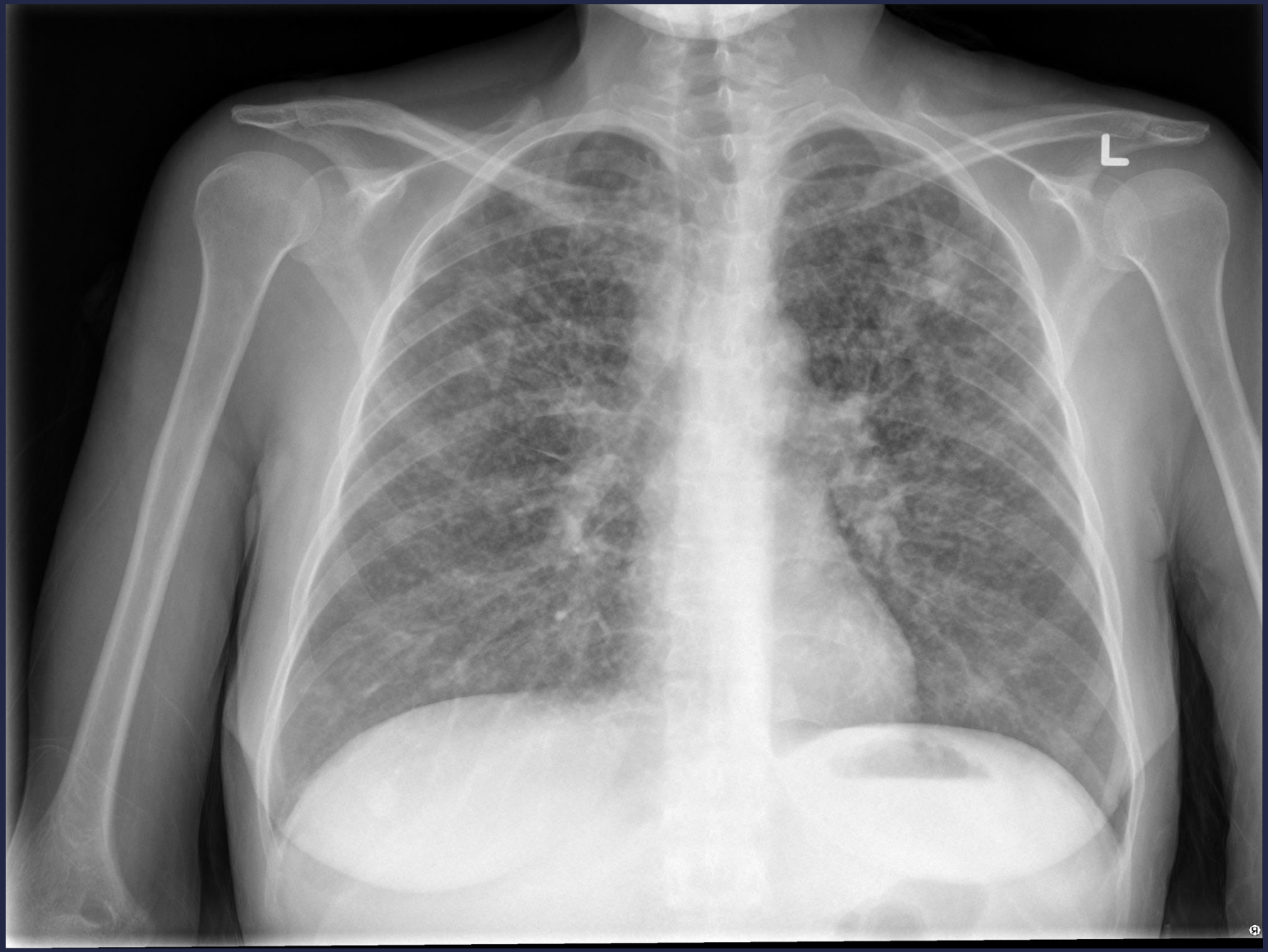
- Started her on crushed Truvada and Sustiva
  - CD4 up to 80, viral load undetectable
  - Eventually she stopped ARV's (unpalatable- sustiva-> yuk!)

- Started crushed truvada and kaletra liquid.

- Then……..

Case 2: Zoe

- 48 year old female, PWID, HIV and HCV positive
  - Cough, fever, weight loss over 1 month, abdominal pain, diarrhea
  - On Exam:
    - Cachectic, T 38 C HR 92 RR 14 BP 124/80 Sats 95% RA
  - Labs:
    - WBC 4 CD4 187 HIV Viral load NA
    - Ast 200 Alt 280 Alp 300 Ggt 380
    - Bilirubin 30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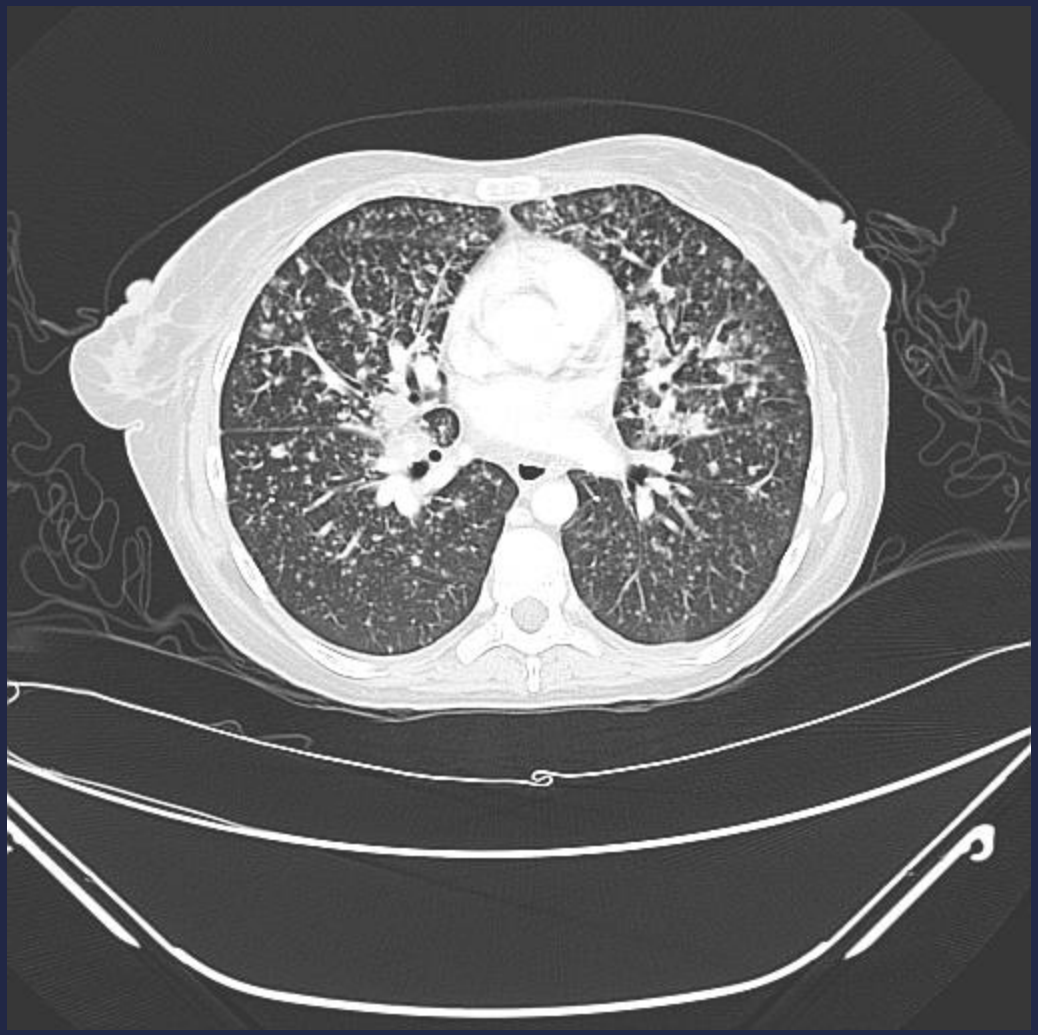
Plan

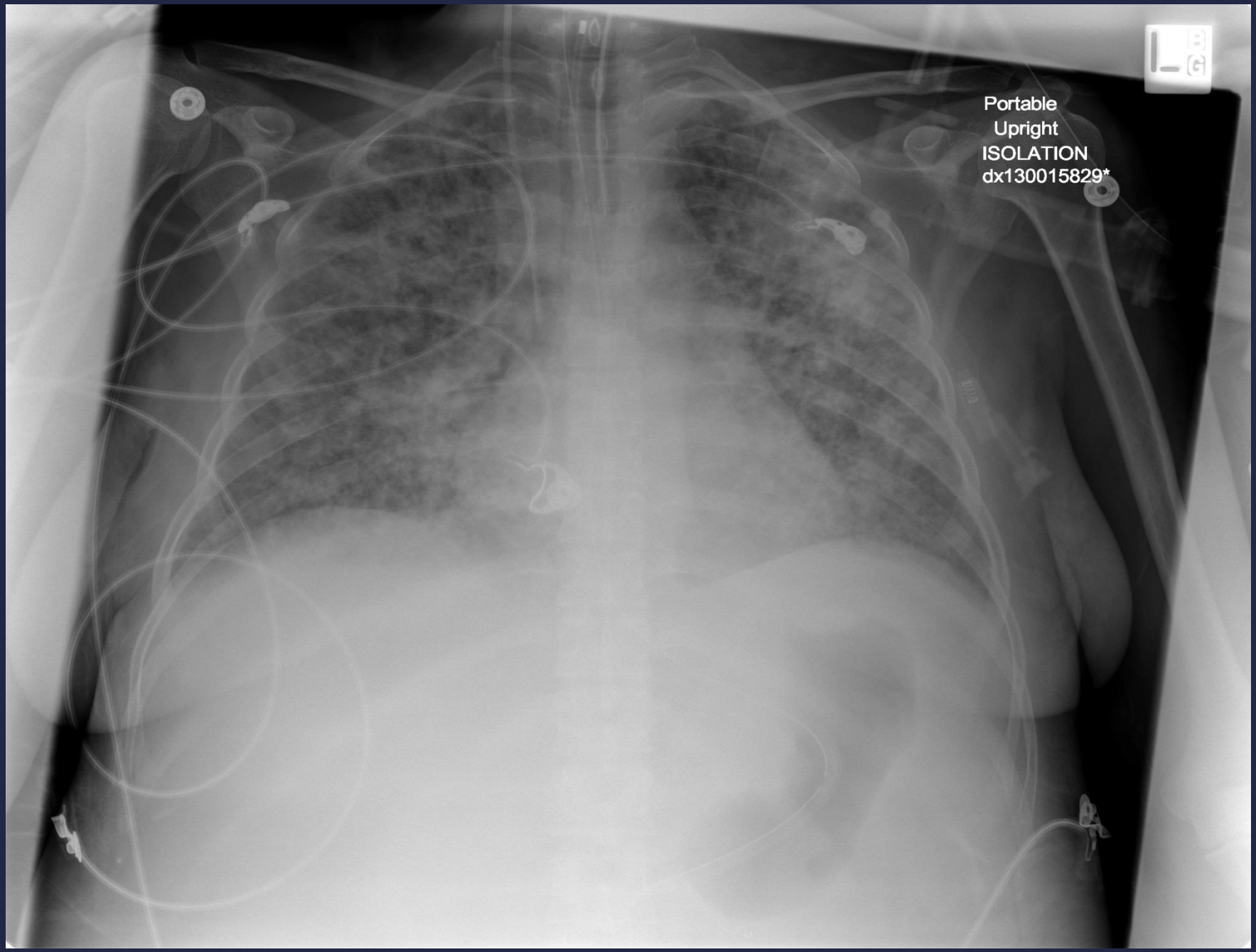
- Admitted locally for sample collection
  - Failed
- To SPH for bronchoscopy
  - En route, decompensated
  - Intubated within 6 hours of arrival

- Sputum 3+ smear positive AFB, also E Coli
- Started on 4 drug daily regimen. IREZ + B6



Complications

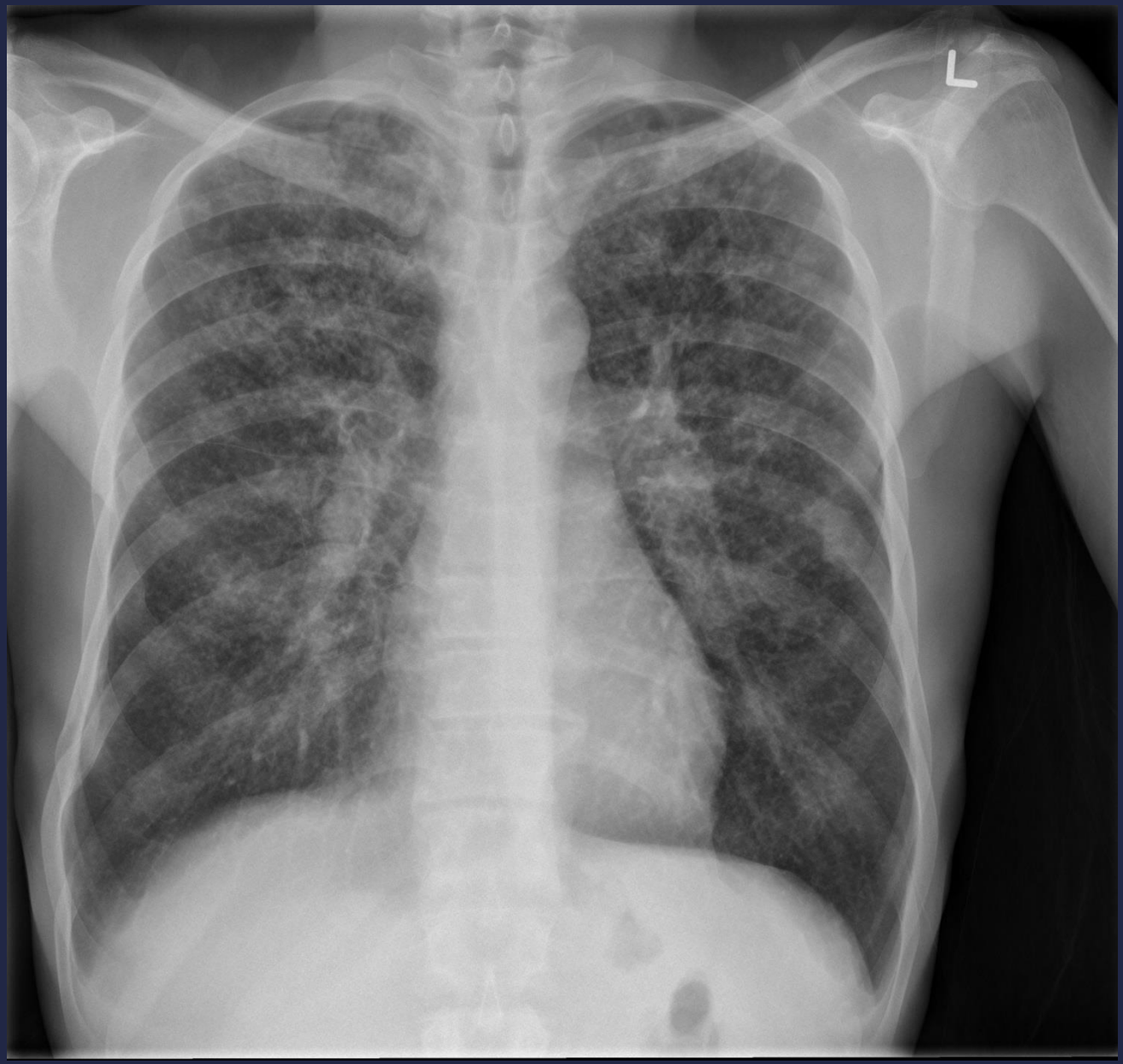
- Acute hepatitis, secondary to HCV and INH toxicity
- GI bleed secondary to abdominal TB
- Prolonged ileus interfering with TB med absorption, and prolonged intubation with persistent smear positivity
- Intravenous TB therapy, severe thrombocytopenia
- Malnutrition, hypoalbumenemia, anasarca
- Multi organ failure and death.


Portable
Upright
ISOLATION
dx130015829*

Steven

- 40 year old male from northern First Nation
- PWID, HIV +, HCV + never treated for either
- Referred to TB control by GP

- Showed 1 month after 1st appointment
  - Minor cough, dry, weakness, fatigue
  - Sats 94% on RA, rr 16, hr 95, bp 124/67
  - Pulmonary crackles , no evidence of extra pulmonary disease
  - CD4 147, liver enzymes mildly elevated, otherwise normal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Probably miliary TB

- He refused to go to hospital!
- Collected sputum and urine for AFB and Tb culture, PJP, Gm Stain C and S, blood cultures.
- Started him on IREZ and TMP/SMX for proph of PJP.
  - Told his methadone prescriber about DI with rifampin
- Called local nurse and asked her to watch him and call me anytime.

Steven

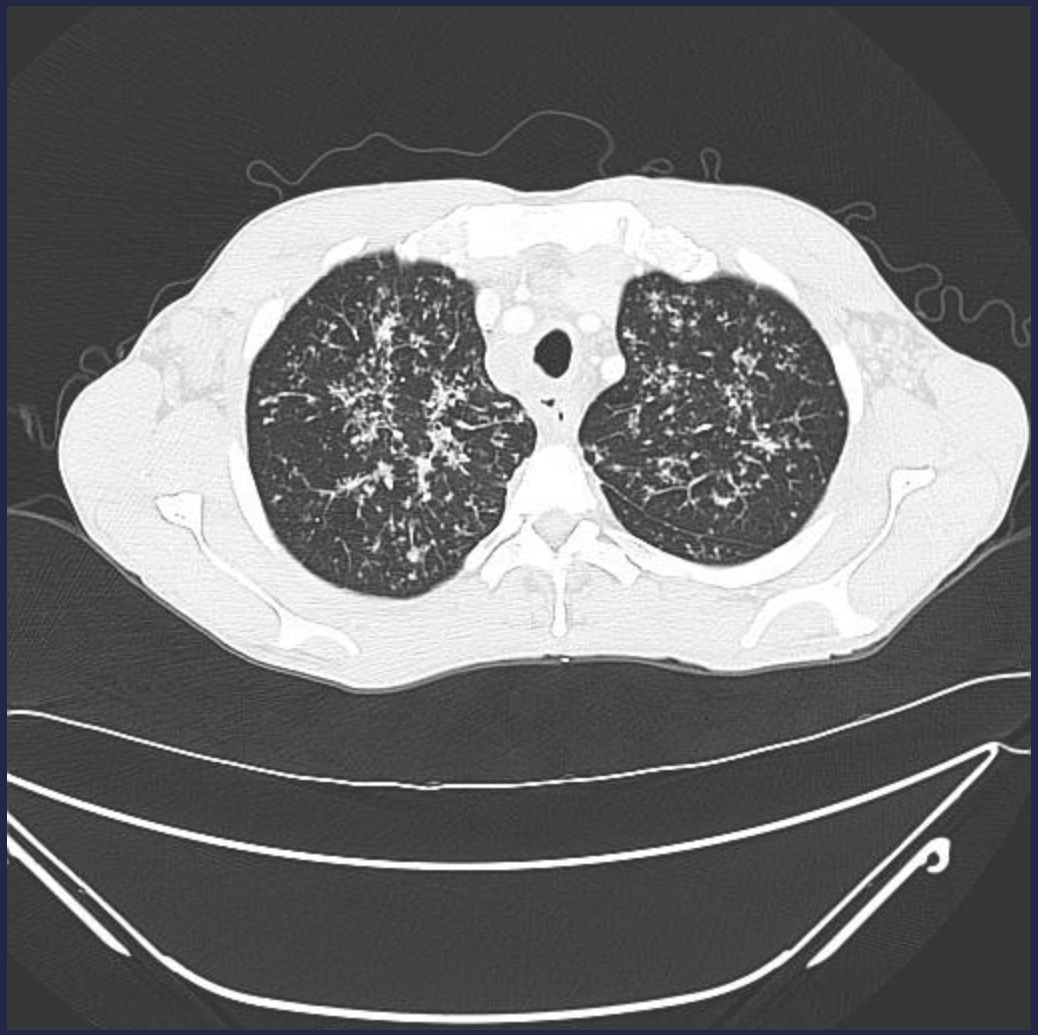
- 2 nights later, frantic call from nurse on reserve.

- Brought to SPH where I work
  - Severe pain, nausea and vomitting!
  - Tachycardic, hypertensive, tachypneic

- Diagnosis?

Steven

- Admitted.
  - Treated with IREZ + TMP/SMX
  - Methadone changed to Kadian
- Developed facial Zoster with erysipelas
  - Started on Valtrex and ancef.
- 9 new drugs within 72 hours.



Steven

- Acute liver and renal failure
  - Ast, Alt > 500
  - Creatinine up to 340
- Stopped everything, waited 5 days……
- CR and enzymes normalized.

Steven

- Started INH and RMP, only
- Liver and kidneys held.
- He went home in a month, started Atripla at about 6 weeks
- Last week, finished his TB treatment, HIV vl undetectable, CD4 400, stable on OST, doing great!

Summary

- TB improving world wide and through out Canada but still a major challenge in Saskatchewan's north.
- Situation complicated by high incidence of HIV and challenges associated with delivering care to population with addiction spread over a large and remote area.
- High rate of HIV TB coinfection with occasionally terrible outcomes.

Summary

- Aggressive contact tracing, case finding for LTBI and prophylaxis underway especially in those with HIV.
  - Use of novel technologies to assist
    - Pima (POC CD4 testing unit)
    - RP-Xpress (Doc in the Box)
- Focus on high incidence communities and creative strategies to improve engagement.

The End