

Recurrent tuberculosis among HIV-coinfected patients: a case series from KwaZulu-Natal

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Background: Recurrent tuberculosis (TB) following TB treatment completion in HIV-infected individuals remains a major public health burden. We assessed the role of various risk factors in mediating the development of recurrent TB and subsequent resistance to antiretroviral therapy and anti-TB drugs.

Patients and methods: We analyzed secondary demographic, clinical, and laboratory data from medical records of five HIV-infected TB patients enrolled between 2009 and 2014 in a prospective observational study investigating TB recurrence. Paired clinical isolates of *Mycobacterium tuberculosis* were typed by IS6110 restriction fragment length polymorphism analysis to determine the mechanism of TB recurrence. Plasma samples were genotyped to determine acquisition of HIV drug resistance mutations on antiretroviral treatment (ART).

Results: All five patients were HIV-coinfected, with a previous history of TB infection and prior exposure to anti-TB treatment, and residual lung damage, and demonstrated poor treatment adherence – significant risk factors linked to the development of recurrent TB disease. Furthermore, three of the five patients had multiple episodes of drug-susceptible TB infection with subsequent drug-resistant TB infection. Genotyping of the initial and recurrent *M. tuberculosis* isolates demonstrated three cases of recurrent TB because of relapse and two because of reinfection. All five patients had no mutations at ART initiation; however, by the end of the study follow-up, all patients developed dual class resistance.

Conclusion: This series demonstrates the complexity of recurrent TB in HIV coinfection. We highlight the challenges of managing coinfecting patients and the increased propensity for the development of drug resistance. We report on the role of various risk factors mediating the development of resistance and subsequent clinical impact. This report underscores the need for structural clinical and adherence interventions for the management of complex treatment and dosing.

Keywords: adherence, TB–HIV coinfection, social risk factors, IS6110 RFLP, drug resistance

Introduction

Globally, tuberculosis (TB) presents as the most common opportunistic infection in people with HIV.¹ In the latest global TB report, the World Health Organization estimated that 10% of the 10.4 million incident cases of TB in 2016 were coinfecting with HIV. Sub-Saharan Africa bears the highest rates of HIV-associated TB, with coinfection rates of up to 50% in some areas.¹ In HIV-uninfected individuals with latent TB infection, the lifetime risk of TB reactivation disease is 10%. This risk is increased to 10% per annum in HIV-infected patients.² In addition to the increased risk of TB reactivation, HIV coinfection has also been reported as a significant risk

factor for recurrent TB disease. Weakened immune responses, a hallmark characteristic of HIV infection, facilitates the progression to active TB disease and is a significant risk factor for recurrent TB disease.³ HIV–TB coinfection is further complicated by the development of drug resistance in *Mycobacterium tuberculosis*.^{4–6}

Recurrent TB disease, following cure or successful treatment completion, occurs as a result of either relapse (recurrence of the previous infection) or reinfection (infection with a new strain type), each associated with its own risk factors. Risk factors associated with individual vulnerability including immune compromise due to comorbidities such as HIV coinfection and diabetes mellitus, residual lung damage due to previous TB infection, age, malnutrition, and social risk factors such as alcohol abuse and cigarette smoking have been attributed to both relapse and reinfection. Risk factors that impact on treatment response such as inadequate treatment regimen, poor treatment adherence, and unrecognized drug resistance or host-specific factors that affect drug metabolism have been attributed to relapse of TB disease. Increased risk due to poor epidemic or infection control resulting in repeat exposure has been attributed to reinfection. Distinguishing between relapse and reinfection requires comparing the homology of *M. tuberculosis* strains isolated during the first and recurrent TB episodes using molecular-based DNA fingerprinting techniques.^{7,8}

Complex multi-drug regimens and optimal medication adherence are required for effective treatment of TB/HIV coinfection.^{9–11} This results in challenges of adherence to complex dosing strategies, long duration of therapy, serious and often life-threatening drug side effects, and drug–drug interactions.¹¹ Adherence, a major factor undermining treatment outcomes, relies on patients' attitude, knowledge, and beliefs, which are in turn influenced by poverty, gender, stigma, and other social and cultural factors.^{9–14} Patients failing TB treatment are likely to remain infectious thereby increasing the likelihood of ongoing transmission of infection.^{9,15,16} We report and analyze five patients with HIV–TB coinfection, receiving concomitant treatment for both diseases and who subsequently developed recurrent drug-resistant TB (DR-TB). This report highlights the various risk factors that contributed to the development of recurrent TB.

Patients and methods

We conducted a retrospective chart review on a subset of patients enrolled in the CAPRISA TRuTH study investigating the incidence of TB recurrence in adult TB/HIV-coinfected patients, who previously completed treatment for drug-sensitive

pulmonary TB in the CAPRISA SAPIt trial.¹⁷ The study was conducted between June 2005 and August 2013. Patients were followed up quarterly for 5 years. Among 82 patients who developed recurrent TB, five patients were diagnosed with recurrent DR-TB. Case notes were used to report the contributing risk factors to the development of recurrent TB.

Patients diagnosed were treated with standard TB treatment, and treatment outcomes were recorded as per the South African National TB control program guidelines.¹⁸ Patients were initiated on a once-daily first-line antiretroviral treatment (ART) regimen and managed as per national guidelines.¹⁹ Participants received TB treatment adherence – counseling occurred prior to TB treatment initiation, and adherence was enhanced and verified through TB directly observed therapy short-course (DOTS) program. ART adherence support occurred through group counseling, two sessions prior to initiation, one on the day of treatment, and continued six-monthly thereafter. Adherence was assessed by clinic-based pill count at all scheduled visits, and six-monthly virologic outcomes. Adherence was described according to previously published categories by medication possession ratios and patient self-reporting.

To determine the mechanism mediating TB recurrence, initial and recurrent isolates were genotyped using the IS6110 restriction fragment length polymorphism method.^{22,23} To assess the impact of HIV on TB recurrence, HIV virologic markers were assessed and stored plasma samples were analyzed for drug resistance conferring mutations prior to ART initiation, at the entry of the TRuTH study, and at the end of the study. HIV drug resistance sequencing incorporated the viral protease (codons 1–99) and reverse transcriptase (codons 1–230) genes. Drug resistance mutations were interpreted using the Stanford University HIV drug resistance database^{16,18} and the International AIDS Society mutation list.¹⁹

Ethical approval for the TRuTH study was obtained from the University of KwaZulu-Natal Biomedical Ethics Research Committee, reference number BF051/09; Clinical trials number NCT01539005. Written informed consent was obtained from all participants to publish case details and images with no personal identifiers.

Results

In-depth clinical profiles for each patient are described in Table 1. The mean age was 34.8 (range, 30–38) years during the first TB episode. Among the five participants, two were female and three were male. One patient displayed a body mass index (BMI) of 17.0, falling within the underweight

Table 1 Epidemiologic and clinical characteristics of five patients with recurrent (M) XDR-TB following drug-susceptible TB

Clinical and epidemiologic biomarker	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	38	32	38	36	30
Gender	M	M	F	F	F
BMI					
BMI at TB-1 diagnosis	19.4	18.7	17.6	21.4	26
BMI at TB-1 end	18.4	20.5	18.7	23.2	26.5
BMI at TB-2 diagnosis	21.3	20.4	17.0	19.4	25.8
Initial episode of TB					
Date and method of diagnosis	Jul 2007 X-ray + sputum	Jul 2007 X-ray + sputum	Jan 2007 X-ray + sputum	Nov 2007 X-ray + sputum	Aug 2005 X-ray + sputum
Genetic and susceptibility profile	Beijing DS-TB	F15/LAM4/KZN DS-TB Lymph aspirate resistant to INH and RIF	F28 DS-TB	F28 DS-TB	Unique DS-TB
Chest radiograph	Infiltrates on RL; cavities and infiltrates on LL	Infiltrates on RL and LL	Cavities, infiltrates, pleural disease, and shrinkage and destruction in RL, minimal fibrosis on LL	Cavities and infiltrates in RL and LL	Cavities and infiltrates in RL and LL
Completion date, duration on treatment and outcome	1 April 2008 8 months Cure	20 March 2008 8 months Cure	20 August 2007 10 months Cure	Jun 30 2008 7 months Cure	02 January 06 6 months Cure
Chest radiograph at the end of treatment	Fibrosis in upper RL	Fibrosis in LL	Extensive fibrosis	Not available	Not available
Recurrent MDR/XDR episode of TB					
Mechanism of recurrence, genetic profile of TB isolates and time to recurrence	Reinfection Beijing to KZN strain 24 months	Relapse KZN strain 28 months	Reinfection F28 – unique 19 months	Relapse F28 strain 28 months	Relapse Unique strain 15 months
Date and method of diagnosis	June 10 X-ray + sputum culture	Feb 2011 X-ray + sputum	Apr 2010 X-ray + sputum culture	Nov 2010 X-ray + sputum	May 07 X-ray + sputum
Susceptibility profile	XDR-TB Resistant to INH, RIF, EMB, kanamycin, capreomycin, OFX, lialiamide, SM, ETH, and PZA	MDR-TB Resistant to INH, RIF, EMB, ETH, PZA, and SM	MDR-TB Resistant to NH, RIF, ETH, SM, and PZA	MDR-TB Resistant to INH, EMB, RIF, SM, ETH, and PZA	XDR-TB INH, RIF, EMB, MXF, KANA, and ETH
Radiologic findings	Infiltrates on RL and infiltrates and new lesions on LL	Cavities in LL	Bullae and plural effusion in RL	Cavities and infiltrates on RL and fibrosis on LL	Cavitation in LL
Treatment outcome	Transferred out for DR-TB care	Transferred out for DR-TB care	Died	Withdrew from study	Transferred out for DR-TB care
HIV history					
Date of diagnosis	Jul 2007	Jul 2007	Jan 2007	Dec 2007	2005
Treatment regimen	AZT/3TC/EFV, switched AZT to TDF in May 2009	ddl/3TC/EFV (discontinued between March and April 2009)	ddl/3TC/EFV	ddl/3TC/EFV switched to ABC/TDF/LPV/r in October 2008, and back to regimen 1 in June 2011	switched to TDF in July 2011

(Continued)

Table 1 (Continued)

Clinical and epidemiologic biomarker	Patient 1	Patient 2	Patient 3	Patient 4	Patient case 5
Regimen response	Virologic suppression; sustained high CD4+ cell count	Raised CD4 count and virologic suppression by Month 12	Good virologic suppression, CD4 cell count remained low	Failed both regimens, placed back onto Regimen 1	Good virologic suppression, CD4 count remained low
CD4/VL at initial TB diagnosis	CD4 =200 VL =260,000	CD4 =54 VL =126,000	CD4 =151 VL =41,663	CD4 =245 VL = Unavailable	CD4 =205 VL =83,900
CD4/VL at the end of first TB episode	CD4 =434 VL =400	CD4 =377 VL ≤400	CD4 =331 VL ≤400	CD4 =212 VL =27,400	CD4 =352 VL ≤400
CD4/VL at recurrent TB diagnosis	CD4 =3,652 VL = unavailable	CD4 =565 V ≤400	CD4 =245 VL ≤40	CD4 =143 VL =20,302	CD4 =204 VL =69,400
Other notes					
TB risk profile	Hospitalization	Hospitalization	Hospitalization	Household TB contacts	No risks
Adherence profile	Poor; adherence support program	Fair; missed clinic visits due to alcohol use, occasional missing of doses	Good	Poor; hospitalization for supervised TB treatment	Good
Other medical conditions	Anemia, PN, SN, HepB	IRIS on TB treatment, PN	PN, pneumonia in August 2010	Hypertension, PN	None
Substance use history	Alcohol abuse, smoking	Alcohol abuse, smoking	None	None	None

Notes: Initial episode of TB = TB-1; Recurrent episode of TB = TB-2 radiological findings from chest x-rays conducted after diagnosis and treatment end (closest date available given).

Abbreviations: 3TC, lamivudine; ABC, abacavir; ALV, alluvia; AZT, azidothymidine; BMI, body mass index; CD4, CD4+ T-cell count (cells/ μL^3); DDI, didanosine; EFV, efavirenz; EMB, ethambutol; ETH, ethionamide; Hep B, hepatitis B; INH, isoniazid; LL, left lung; MDR, multi-drug-resistant; OFX, ofloxacin; PN, peripheral neuropathy; PTB, pulmonary TB; PZA, pyrazinamide; R4, Rifampin; RIF, rifampicin; RL, right lung; SM, streptomycin; SN, sensory neuropathy; TB, tuberculosis; TDF, tenofovir; VL, viral load (copies/ μL^3); XDR, extensively drug-resistant.

range during the recurrent TB episode. The remaining patients recorded BMI values in the normal range.

TB history and associated risk factors for recurrent TB

All five patients had a previous history of TB disease for which they received between 6 and 10 months of DS anti-TB treatment, before enrolling into the TRuTH study. Patients 1 and 5 subsequently developed XDR-TB, and the remaining patients developed MDR-TB. Patients 1, 2, and 3 presented with DR-TB in the TRuTH study 24, 28, and 19 months, respectively, after successful treatment completion for two prior episodes of DS-TB. Patients 4 and 5 presented with DR-TB during the TRuTH study 28 and 15 months, respectively, after successful treatment completion for one episode of DS-TB. Assessment of radiographic chest X-rays during initial TB infection, point of cure for initial TB episode, and TB relapse (Figures S1–S4 and Table 1) indicated that recurrent TB infection was characterized by the presence of vast damage to the lungs and residual damage from prior TB infection. Month 2 sputum culture results were only available

for patients 1 and 2, both of which remained positive. The remaining patients had only sputum smear results available, all of which were negative. Among the paired *M. tuberculosis* isolates representing the initial and recurrent TB episodes, there were two cases of TB reinfection (patients 1 and 3) and three cases of TB relapse (patients 2, 4, and 5). Detailed data on genetic profiles, drug susceptibility profiles, and timelines for recurrent disease episodes are reported in Table 1.

HIV coinfection and its impact on recurrent TB disease

All five patients were diagnosed with HIV at screening of the SAPIt trial and initiated on standard treatment at various points during concomitant anti-TB therapy. The mean CD4+ T cell count was 171 cells/ mm^3 at diagnosis of the initial TB episode, 341,2 cells/ mm^3 at cure of the first TB episode and 289 cells/ mm^3 at diagnosis of recurrent TB. CD4 and viral load data for each patient are detailed in Table 1. Retrospective analysis of HIV drug resistance mutations demonstrated that the patients had no pre-ART drug resistance mutations. However, over the course of treatment and

subsequent regimen changes, by the end of the study all patients developed dual class resistance with non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations featuring prominently. Protease inhibitor resistance mutations were not detected in any of the patients described. Detailed data on all resistance-associated mutations over the course of treatment are shown in Table 2.

Adherence and social risk factors

There were various social risk factors and treatment adherence issues that played a role in the complex clinical course of these patients. Patient 1 had a history of alcohol abuse resulting in poor adherence, missed clinic visits, and discontinuation of ART for a period of 6 months. The patient's hospital admission also coincided with diagnosis of his recurrent TB episode. Patient 2 also had a reported history of alcohol abuse resulting in poor adherence and incarceration that coincided with his MDR-TB diagnosis. Patient 3 reported that her partner was HIV positive who was not on ART and declined condom use with her. In addition, this patient reported a low level of educational attainment. Patient 4 displayed poor adherence despite receiving intensive counseling under study conditions. She also reported close contacts with TB patients, no condom use, and low level of educational attainment. Patient 5 reported no significant adherence or social risk factors.

Discussion

This series highlights the impact of various risk factors in the development of recurrent TB infection in five HIV-coinfected patients. We further highlight the considerable complexity in the management of coinfecting patients because of the use of multiple drugs with complex dosing schedules, and prolonged treatment course that is often complicated by severe overlapping drug toxicities. Published data from various settings consistently demonstrate the impact of these factors on patient adherence and retention in care.^{20,21,24,25}

Notwithstanding the small sample size in this case series, the following important findings should be noted. All five patients were HIV coinfecting with a previous history of TB infection and prior exposure to anti-TB treatment, residual lung damage, and demonstration of poor treatment adherence; significant risk factors linked to the development of recurrent TB disease. Furthermore, three of the five patients had multiple episodes of DS-TB infection with subsequent DR-TB infection. Strain typing revealed that recurrence occurred by relapse in three cases and by reinfection in two cases. While published reports

attribute reinfection as the main mechanism of recurrence in the context of HIV coinfection, we demonstrated three cases of relapse in our study among HIV/TB-coinfected patients.²⁶⁻²⁹ Furthermore, our data support findings of a recent South African study showing ongoing transmission of DR-TB, and the low rates of TB culture conversion including frequent reversion.⁶

We retrospectively analyzed the development of ART resistance mutations in our recurrent TB patients. Despite having no mutations at ART initiation, by the end of the study all five patients developed dual class resistance with NNRTI mutations featuring prominently. The considerable pill burden imposed by the addition of DR-TB treatment to chronic ART is likely to have negatively impacted ART adherence fueling development of ART resistance. These findings are consistent with the published surveillance studies conducted in this setting, reporting the mutations detected in this study as prevalent mutations associated with acquired resistance in adults.^{15,30-34} Retrospective analysis of the resistance mutations reveals that patients were receiving inadequate ART for optimal viral suppression. Furthermore, guidelines advocate first-line ART regimen switch without the benefit of ART resistance testing. This coupled with the lack of objective markers of ART adherence comprises early detection and management of ART failure. Most importantly, these cases highlight the need for ongoing clinical monitoring for treatment failure and HIV resistance testing, especially in patients taking complex regimen for multiple concurrent conditions.

Suboptimal adherence to treatment was a key factor driving drug resistance in this subset of patients. Despite receiving enhanced counseling support under clinical trial conditions, patients remained nonadherent. In keeping with previous reports, known behavioral and biologic risk factors such as alcohol misuse, incarceration, hospital admission, poor pill-taking behavior, low level of education attainment, and missed clinic appointments featured among patients failing treatment and acquiring resistance in this study. Despite access to free care for both HIV and TB, underlying social issues severely impacted treatment outcomes underscoring the need for strong ongoing support directed at optimizing treatment adherence and treatment completion.^{9,14,16,35-39} DOTS programs played a pivotal role in increasing treatment completion rates globally. Adopting a similar strategy for the management of DR-TB and HIV coinfection could impact on reducing recurrent TB rates.⁴⁰⁻⁴² As reinfection rates are higher in HIV endemic settings like South Africa, we also highlight the need for enhanced infection control measures

Table 2 HIV drug resistance profiles at TRUTH study entry and exit visits

	ART regimen	Drug resistance mutations at TRUTH entry	Drug resistance mutations at the end of TRUTH study
Patient 1	AZT/3TC/EFV switched to TDF/3TC/EFV	NRTI: D67N; K70R; M184V; T215P; K219E NNRTI: V106M; Y188P; M230L	NRTI: M184V NNRTI: K103N; G190A; Y188L
Patient 2	ddl/3TC/EFV	None	NRTI: M184V NNRTI: V106M; Y188L
Patient 3	ddl/3TC/EFV	NRTI: T215S ^b NNRTI: K103N	NRTI: K70E; M184V NNRTI: K103N
Patient 4	ddl/3TC/EFV switched to ABC/TDF/LPV/r then switched back to ddl/3TC/EFV	None	NRTI: M184V NNRTI: K101E; K103N; G190A
Patient 5	ddl/3TC/EFV switched to TDF/3TC/EFV	None	NRTI: M184I NNRTI: V106M; Y188C; H221Y

Notes: ^aRevertant mutation; ^bTransitional mutation. None of the patients had any resistance associated mutation prior to the initiation of treatment.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ddl, didanosine; AZT, zidovudine; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; LPV/r, lopinavir-boosted ritonavir (Aluvia; Abbott, South Africa).

and ongoing surveillance in congregate settings such as clinic waiting rooms, hospitals, and prisons.^{43,44}

We would like to acknowledge study limitations. Secondary study data and stored samples from the study biorepository were analyzed. We had to rely on self-reported information regarding prior ARV treatment and ART and TB adherence. The lack of availability of objective markers of adherence undermines our ability to understand the evolution of drug resistance to ART and TB drugs. Furthermore, the small sample size limits the generalizability of our findings to other patients and settings. We also did not establish if these patients had mixed strain infection and the extent to which this might have influenced our findings.

In conclusion, the cases described in this series highlight the public health crisis resulting from the intersecting epidemics of DR-TB and drug-resistant HIV. The study underscores the complexity of managing TB and HIV coinfection, and the impact of various risk factors in mediating resistance. Patients failing treatment present a public health risk of ongoing transmission of resistant strains. Distinguishing between relapse and reinfection plays an invaluable role in addressing the burden of recurrent TB disease. High rates of relapse underscore the need for renewed interventions to improve individual patient care while high rates of reinfection underscore the need for improved epidemic control measures. Urgent attention is also required to address challenges of adherence, such as social and health care worker support systems and step-down management facilities. Enhanced treatment options, such as intensified initial treatment, extension of treatment, and preventative therapy for patients presenting with multiple risk factors, will prevent recurrent TB infection. The heightened risk of recurrent TB in ART programs underscores the need for regular TB screening at

ART follow-up visits. There has been considerable disparity in the studies reporting on the role of relapse vs reinfection. Further large-scale studies are required to address the role of relapse and reinfection as well as the role of mixed infections in recurrent TB.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Chest radiographs for Patients 1–4 (no images available for Patient 5).

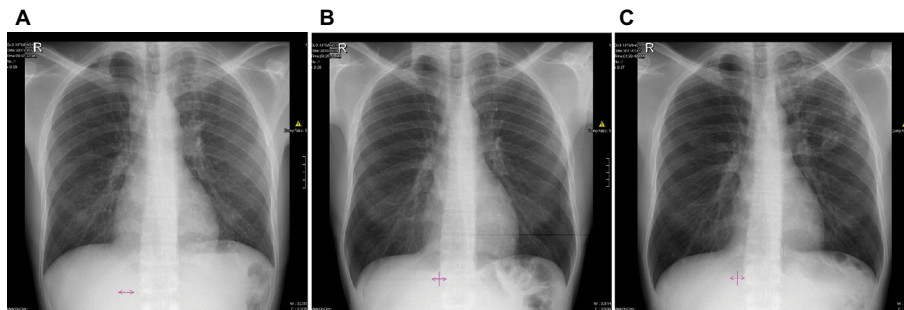


Figure S1 Chest X-rays of Patient 1 depicting (A) infiltrates on both lungs; (B) persistent fibrosis in the left lung; and (C) cavities in the left lung.

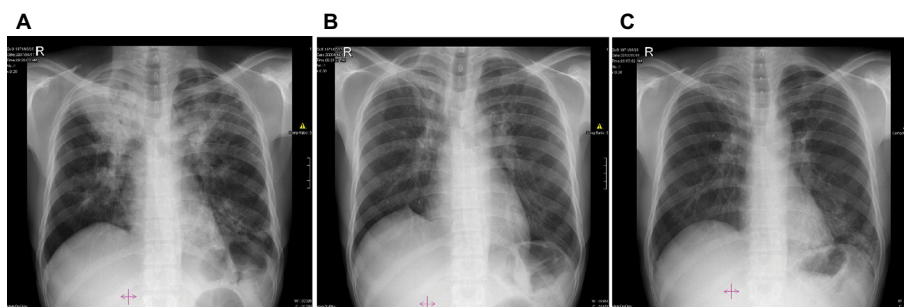


Figure S2 Chest X-rays of Patient 2 depicting (A) infiltrates in both lungs and cavities in the left lung; (B) right upper lobe fibrosis; and (C) infiltrates in the right lung and infiltrates and new lesions in the left lung.

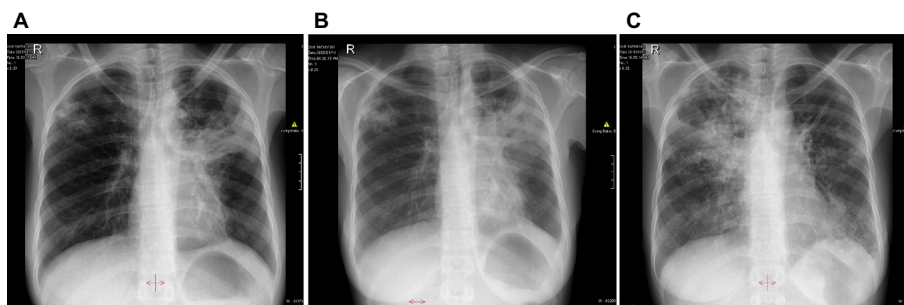


Figure S3 Chest X-rays of Patient 3 depicting (A) cavities and infiltrates in both lungs; (B) cavities and infiltrates on the right lung and fibrosis in the left lung; and (C) cavities, infiltrates, and patchy consolidation in the right lung and consolidation in mid and lower zones of the left lung.

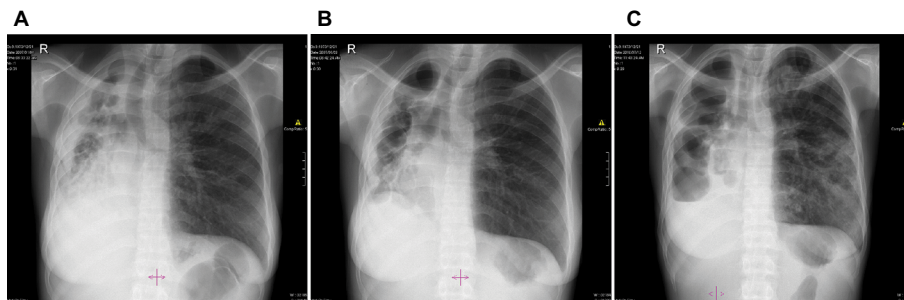


Figure S4 Chest X-rays of Patient 4 depicting (A) vast damage to the right lung with cavities, infiltrates, pleural disease, shrinkage, and destruction. Minimal damage to the left lung; (B) residual widespread damage to the right lung; and (C) right lung bullae and new pleural effusion. New infiltrates in left lung.

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