HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2017 July 19.

Published in final edited form as:

N Engl J Med. 2017 January 19; 376(3): 243–253. doi:10.1056/NEJMoa1604544.

Transmission of Extensively Drug-Resistant Tuberculosis in South Africa

N. Sarita Shah, M.D., M.P.H., **Sara C. Auld, M.D.**, **James C.M. Brust, M.D.**, **Barun Mathema, Ph.D.**, **Nazir Ismail, Ph.D.**, **Pravi Moodley, M.D.**, **Koleka Mlisana, M.D., Ph.D.**, **Salim Allana, M.B., B.S., M.D.**, **Angela Campbell, M.A.**, **Thuli Mthiyane, M.Sc.**, **Natashia Morris, M.Sc.**, **Primrose Mpangase, B.A.**, **Hermina van der Meulen**, **Shaheed V. Omar, Ph.D.**, **Tyler S. Brown, M.D.**, **Apurva Narechania, M.A.**, **Elena Shaskina, Ph.D.**, **Thandi Kapwata, M.Sc.**, **Barry Kreiswirth, Ph.D.**, and **Neel R. Gandhi, M.D.**

Emory University Rollins School of Public Health and School of Medicine (N.S.S., S.C.A., S.A., A.C., N.R.G.) and the Centers for Disease Control and Prevention (N.S.S.) — both in Atlanta; Albert Einstein College of Medicine and Montefiore Medical Center (N.S.S., J.C.M.B., N.R.G.), Columbia University Mailman School of Public Health (B.M., T.S.B.), and the American Museum of Natural History (A.N.) — all in New York; the National Institute for Communicable Diseases, Johannesburg (N.I., H.M., S.V.O.), University of KwaZulu-Natal and National Health Laboratory Service, Durban (P. Moodley, K.M., T.M., P. Mpangase), and the South African Medical Research Council, Cape Town (N.M., T.K.) — all in South Africa; and the Public Health Research Institute, New Jersey Medical School–Rutgers University, Newark (E.S., B.K.)

Abstract

BACKGROUND—Drug-resistant tuberculosis threatens recent gains in the treatment of tuberculosis and human immunodeficiency virus (HIV) infection worldwide. A widespread epidemic of extensively drug-resistant (XDR) tuberculosis is occurring in South Africa, where cases have increased substantially since 2002. The factors driving this rapid increase have not been fully elucidated, but such knowledge is needed to guide public health interventions.

METHODS—We conducted a prospective study involving 404 participants in KwaZulu-Natal Province, South Africa, with a diagnosis of XDR tuberculosis between 2011 and 2014. Interviews and medical-record reviews were used to elicit information on the participants' history of tuberculosis and HIV infection, hospitalizations, and social networks. *Mycobacterium tuberculosis* isolates underwent insertion sequence (IS)*6110* restriction-fragment– length polymorphism analysis, targeted gene sequencing, and whole-genome sequencing. We used clinical and genotypic case definitions to calculate the proportion of cases of XDR tuberculosis that were due to inadequate treatment of multidrug-resistant (MDR) tuberculosis (i.e., acquired resistance) versus those that were due to transmission (i.e., transmitted resistance). We used social-network analysis to identify community and hospital locations of transmission.

Address reprint requests to Dr. Gandhi at the Rollins School of Public Health, Emory University, 1518 Clifton Rd. NE, Claudia Nance Rollins Bldg., Rm. 3031, Atlanta, GA 30322, or at neel.r.gandhi@emory.edu.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

RESULTS—Of the 404 participants, 311 (77%) had HIV infection; the median CD4+ count was 340 cells per cubic millimeter (interquartile range, 117 to 431). A total of 280 participants (69%) had never received treatment for MDR tuberculosis. Genotypic analysis in 386 participants revealed that 323 (84%) belonged to 1 of 31 clusters. Clusters ranged from 2 to 14 participants, except for 1 large cluster of 212 participants (55%) with a LAM4/KZN strain. Person-to-person or hospital-based epidemiologic links were identified in 123 of 404 participants (30%).

CONCLUSIONS—The majority of cases of XDR tuberculosis in KwaZulu-Natal, South Africa, an area with a high tuberculosis burden, were probably due to transmission rather than to inadequate treatment of MDR tuberculosis. These data suggest that control of the epidemic of drug-resistant tuberculosis requires an increased focus on interrupting transmission. (Funded by the National Institute of Allergy and Infectious Diseases and others.)

Drug-resistant tuberculosis is a major global epidemic, with a half million cases occurring each year.[1] Extensively drug-resistant (XDR) tuberculosis — the most severe form of drug resistance — has been reported worldwide and involves resistance to at least four first-line and second-line drugs for tuberculosis. This high degree of resistance severely limits treatment options, necessitating the use of complex, toxic, and costly regimens. Rates of treatment success are less than 40% in most patient populations, and rates of death are 50 to 80%.[2–6]

Drug-resistant tuberculosis has traditionally been thought to develop as a result of selection pressure that occurs with inadequate treatment of tuberculosis, incomplete adherence to treatment, or subtherapeutic drug levels (“acquired resistance”). The high degree of resistance in XDR tuberculosis can develop only after multiple episodes of ineffective treatment, including the use of second-line drugs for multidrug-resistant (MDR) tuberculosis. However, XDR tuberculosis may also be caused by direct infection with a resistant strain. Transmission of drug-resistant tuberculosis strains (“transmitted resistance”) has been well described throughout the world.[6–11]

Although treatment for XDR tuberculosis does not differ according to its cause, interventions to prevent acquired versus transmitted disease differ. Acquired drug resistance can be reduced by providing effective treatment and ensuring completion of treatment. Halting transmission requires identifying and separating infectious patients, improving ventilation in congregate settings, and promptly initiating of effective treatment. Given the extremely high mortality associated with this disease, especially among patients with human immunodeficiency virus (HIV) coinfection, prevention of XDR tuberculosis is critical. Yet, few studies have quantified the proportion of cases that are due to transmission, and data from geographic areas where HIV infection is highly prevalent are lacking.

South Africa has one of the highest burdens of tuberculosis and drug-resistant tuberculosis in the world. In the past decade, the number of cases of XDR tuberculosis has increased by a factor of 10, to more than 1500 cases in 2012.[12] Compounding the tuberculosis epidemic is the concurrent epidemic of HIV infection; rates of coinfection exceed 70%, and rates of long-term survival among patients with XDR tuberculosis and HIV infection are less than 20%.[2] In this study, we sought to quantify the role of transmission and to elucidate how and where transmission is occurring. We combined traditional epidemiologic tools with social-

network, geospatial, and genotyping methods to describe population-level transmission of XDR tuberculosis.

Methods

Patient Population

We conducted a prospective study involving patients with a diagnosis of culture-confirmed XDR tuberculosis between 2011 and 2014 in KwaZulu-Natal Province, South Africa. KwaZulu-Natal has a population of 10.3 million persons, the majority of whom live in rural areas. The province has nearly half the XDR tuberculosis burden and, according to two reports from the government of South Africa, the highest rates of tuberculosis (1076 cases per 100,000 population) and HIV infection (prevalence, 16.9%) in South Africa.[13,14]

A single provincial referral laboratory conducts all drug-susceptibility testing. During the study period, drug-susceptibility testing was recommended for patients with newly diagnosed tuberculosis who did not have a response after 2 months of treatment, patients with recurrent tuberculosis, and patients with rifampin resistance detected with the use of the Xpert MTB/RIF assay.

Study Design and Oversight

We recruited all persons with newly diagnosed XDR tuberculosis who were residing in KwaZulu-Natal. Written informed consent was obtained from all participants or from the next of kin of deceased or severely ill participants. Interviewers collected information about the participants' sociodemographic characteristics and history of tuberculosis and HIV infection, as well as the location and duration (month and year) of hospitalizations in the preceding 5 years.

Participants were asked to name contacts at home and work with the use of structured social-network questionnaires[15,16] and to state whether each contact currently or previously had tuberculosis or XDR tuberculosis. Participants were asked to enumerate community locations where they spent 2 or more hours per week and contacts at those sites. A global-positioning-system coordinate for each participant's home was obtained and was plotted with the use of ArcGIS software.

Participants with unknown HIV status were offered HIV testing and were referred for care if the results were positive for HIV. CD4+ cell counts and viral loads were tested in participants with HIV infection. Medical records were obtained from the diagnosing facility and any tuberculosis specialty hospitals where the participant had been admitted. Records were reviewed for previous treatment with any antituberculosis medication — including for indications other than tuberculosis — and previous results of drug-susceptibility testing.

The study was approved by the institutional review boards of Emory University, Albert Einstein College of Medicine, and the University of KwaZulu-Natal and by the Centers for Disease Control and Prevention.

Laboratory Methods

A diagnostic XDR tuberculosis isolate was obtained from all participants. Isolates underwent insertion sequence (IS)*6110* restriction-fragment–length polymorphism (RFLP) genotyping and targeted sequencing of eight resistance-conferring regions for rifampin, isoniazid, pyrazinamide, fluoroquinolones, and second-line injectable drugs. These regions were *rpoB, katG, inhA, pncA, gyrA, rpsL, rrs*, and *gidB*.[17] A subset of 298 isolates underwent paired-end whole-genome sequencing. (Details are provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Acquired versus Transmitted Resistance

We used a clinical case definition to determine whether XDR tuberculosis developed in participants because of acquired resistance or transmission. Participants who met any of the following criteria were considered to have XDR tuberculosis that developed through acquired resistance: self-report of treatment for MDR tuberculosis 30 or more days before the diagnosis of XDR tuberculosis, a medical record documenting treatment for MDR tuberculosis before the diagnosis of XDR tuberculosis, a medical record documenting 10 or more days of treatment with second-line antituberculosis drugs for indications other than tuberculosis, or any previous results of drug-susceptibility testing showing resistance to isoniazid and rifampin but susceptibility to fluoroquinolones or second-line injectable drugs (i.e., MDR tuberculosis or pre-XDR tuberculosis). Participants who did not meet any of these criteria were classified as having XDR tuberculosis that developed because of transmitted resistance.

We also developed a genotypic case definition to differentiate acquired resistance from transmitted resistance. *Mycobacterium tuberculosis* isolates with RFLP patterns within a 1-band difference and identical targeted gene sequencing for *inhA, katG, rpoB, pncA*, and *gyrA* were considered to compose a genotypic cluster and to be due to transmission. Unmatched isolates were considered to be unique and to be due to acquired resistance. Pairwise single-nucleotide polymorphism (SNP) data from whole-genome sequencing were used to validate the genotypic case definition (Fig. S1 in the Supplementary Appendix).

In addition to estimating transmission rates according to each definition alone, we combined them to determine a minimum estimate of cases that arose owing to transmission with high certainty. These were cases of XDR tuberculosis in participants who had not received previous treatment for MDR tuberculosis and who had isolates that clustered according to genotype.

Characterization of Transmission Networks

We analyzed social-network data to determine epidemiologic links among participants. Person-to-person links included two enrolled participants who directly named each other or named the same contact. Link Plus software was used to match persons according to name, age, and sex.[18]

We identified overlapping hospitalizations during which at least one participant was in a "vulnerable period," defined as 1 or more months before the diagnosis of XDR tuberculosis (according to the sputum collection date). Participants with overlapping hospitalizations with another participant during their vulnerable period were considered to have a hospital-based link. We also analyzed data regarding other congregate locations named by the patients. We compared genotypes among participants within epidemiologic networks.

Statistical Analysis

We analyzed demographic and clinical characteristics using descriptive statistics, t-tests, the chi-square test, and Fisher's exact test. We used UCINET software for social-network analysis of person-to-person and hospital links.[19] The geographic representativeness of participants with XDR tuberculosis who were enrolled in the study was assessed by comparing their diagnosing health facility with the diagnosing health facility of patients who were not enrolled. All the authors vouch for the completeness and accuracy of the data and analysis presented.

Results

Participants

From May 2011 through August 2014, a total of 1027 patients had a diagnosis of XDR tuberculosis in KwaZulu-Natal (incidence, 3.1 cases per 100,000 population). These diagnoses were made at 212 health care facilities that were located across all 11 districts of the province.

We screened a convenience sample of 521 patients with XDR tuberculosis (51%) and obtained written informed consent from 404 patients (39%) (Fig. 1A). Reasons for nonenrollment were the following: 72 patients declined to participate, 29 patients could not be reached, 8 patients died and did not have next of kin, and 8 patients had other reasons for nonenrollment. The geographic distribution of enrollees did not differ significantly from the overall distribution of patients with a diagnosis of XDR tuberculosis (P = 0.70). Among enrolled participants, 234 were female (58%), the median age was 34 years (interquartile range, 28 to 43), and 50% lived in rural areas (Table 1). A total of 311 participants (77%) had HIV infection, of whom 236 (76%) were receiving antiretroviral therapy. The median CD4+ count was 340 cells per cubic millimeter (interquartile range, 117 to 431), and 155 participants (50%) had an undetectable viral load. A sputum smear for acid-fast bacilli was positive in 270 participants (67%), and 70 participants (17%) had cavitary disease. Forty-four participants (11%) died before study enrollment, and a family member provided consent for study enrollment.

Acquired versus Transmitted Resistance

A total of 124 participants (31%) had been previously treated for MDR tuberculosis, and XDR tuberculosis was presumed to have developed through acquired resistance, according to the clinical case definition (Fig. S2 in the Supplementary Appendix). Treatment outcomes of the previous MDR tuberculosis episode were cure or completed treatment in 6% of the participants, treatment failure in 84%, and loss to follow-up or transfer in 10% (Table 1).

None of the participants received a fluoroquinolone or injectable antibiotics for 10 days or more for indications other than tuberculosis. XDR tuberculosis developed in the remaining 280 participants (69%) through transmission of an XDR tuberculosis strain.

IS*6110* RFLP and targeted gene sequencing were completed in *M. tuberculosis* isolates obtained from 386 participants (96%). Of these isolates, 323 (84%) had a genotype that matched that of an isolate from another study participant (Fig. S2 in the Supplementary Appendix). The matching isolates formed 31 clusters that ranged in size from 2 to 14 participants, with the exception of one large cluster of 212 participants (55%) with the LAM4/KZN strain (Table S1 in the Supplementary Appendix). Within clusters, the median pairwise SNP difference was 5 SNPs to the closest participant (interquartile range, 3 to 8) and 16 SNPs among all cluster members; whole-genome sequencing could not further divide the LAM4/KZN cluster into subclusters (Fig. 2).

According to the combined clinical and genotypic case definitions, 61% of the participants had not received previous treatment for MDR tuberculosis and their isolates were part of a genotypic cluster; this percentage is a minimum estimate of the proportion of participants with XDR tuberculosis that developed through transmission (Fig. S2 in the Supplementary Appendix). An additional 8% of the participants had not received previous treatment for MDR tuberculosis, but their isolates did not have a genotype that matched that of another study participant, and 23% of the participants had received treatment for MDR tuberculosis, but their isolates were clustered with at least one other study participant. XDR tuberculosis may have developed because of transmission in both these groups of participants as well.

Social-Network Analysis

We identified person-to-person or hospital-based epidemiologic links in 123 participants (30%). A total of 2901 contacts were named (median contacts per participant, 7; interquartile range, 4 to 10). The majority of contacts were household members (2301 of 2901 contacts, 79%); 376 contacts were from workplaces (13%), and 224 contacts were from other community settings (8%) such as a church. Among named contacts, 293 were reported to have had tuberculosis (10%) and 25 were reported to have had XDR tuberculosis (1%). Thirteen of these 25 participants were enrolled in this study.

A person-to-person link was identified in 59 of 404 participants (15%) who formed 25 social networks (Fig. 3). A total of 111 connections linked these 59 participants; 93 links (84%) were to household members, 8 (7%) were to persons in workplaces, and 10 (9%) were to persons in other community settings. Certain networks spanned multiple homes, family generations, and community settings (Fig. S3A and S3B in the Supplementary Appendix).

A total of 298 of the study participants (74%) reported having been hospitalized in the 5 years before study enrollment; of these participants, 86 (29%) were hospitalized at more than one hospital. Participants were admitted to 53 different hospitals (Fig. 1B). The median duration of hospitalization was 2 months (interquartile range, 1 to 4).

Among the 298 participants who were hospitalized, 117 (39%) were admitted before they received a diagnosis of XDR tuberculosis. Seventy-one of these 117 participants (61%) had

a hospital-based link with another study participant (Fig. S3C in the Supplementary Appendix). The median number of participants with whom hospitalizations overlapped was 3 (interquartile range, 1 to 18) for a median of 1 month (interquartile range, 1 to 2).

A total of 177 other locations were reported by 124 participants (31%) as sites where they spent substantial time. These sites were 73 churches, 43 bars, 10 beauty salons, 9 prisons, 7 restaurants, 6 nightclubs, and 29 other locations. No locations were named by 2 or more participants to suggest a direct link.

Combined Analysis of Epidemiologic and Genotyping Data

Among the 123 participants with an epidemiologic link (30%), 112 had an isolate available for genotyping. Of these participants, 79 isolates (71%) had a matching RFLP pattern and 39 (35%) were in a genotypic cluster (RFLP plus targeted sequencing) with one of their links. In 21 person-to-person networks, genotyping was available for at least 2 participants. A matching RFLP pattern was seen in 15 of these networks (71%), of which 10 (48%) were in a genotypic cluster. Of the 71 participants with hospital-based links, 46 (65%) had isolates with a matching RFLP and 19 (27%) had isolates that were in a genotypic cluster.

Discussion

In the interval since XDR tuberculosis was first described globally and in South Africa,[6,20] the XDR tuberculosis epidemic in South Africa has continued unabated. The incidence of XDR tuberculosis in South Africa (2.8 cases per 100,000 population) is on par with the incidence of all forms of tuberculosis in the United States,[21] despite substantial efforts to expand access to treatment for MDR tuberculosis, improve cure rates of tuberculosis, and scale up rapid diagnostic testing.

In this study, we examined the role of transmission in the ongoing epidemic of XDR tuberculosis by combining multiple genotyping methods with social-network and epidemiologic analysis. We found that XDR tuberculosis remains widespread throughout KwaZulu-Natal and that transmission is the primary driver of the epidemic. Inadequate treatment of MDR tuberculosis accounted for, at most, 31% of cases of XDR tuberculosis. Genotyping methods also showed the clonal nature of this epidemic and provide further support for the predominant role of transmission. Social-network analysis showed connections among participants with XDR tuberculosis; these connections created numerous opportunities for transmission not only in hospitals, but also in community settings. Our finding of the role of transmission in the epidemic of XDR tuberculosis provides insight as to why the epidemic continues, at least in this community, as efforts to control tuberculosis to date have not sufficiently addressed the interruption of transmission.[22,23]

In our study, we enrolled a cohort of participants with XDR tuberculosis and assessed their *M. tuberculosis* isolates and medical records. At least 69% of the cases of XDR tuberculosis were attributable to transmission, and 84% clustered according to genotype with another participant. Participants were enrolled from a wide geographic area, and half were from rural areas. The results of whole-genome sequencing provide support for these findings, with a median difference of 5 SNPs between the most closely connected patients in each cluster;

these findings are similar to published thresholds for transmission of *M. tuberculosis*.[24–27] Our study results expand on previous studies from South Africa and countries with a low prevalence of HIV infection, such as China, Russia, and countries in the former Soviet Union.[17,28–33] Moreover, our study design, which captured isolates from a large number of cases of XDR tuberculosis over a 4-year period, overcame limitations of previous studies that were not able to show the role of transmission.[34]

Despite the broad geographic area and incomplete enrollment of all the patients in whom XDR tuberculosis was diagnosed, we identified epidemiologic links among 30% of participants. Networks included multiple households and hospitals, in addition to person-to-person links among schoolmates and church members. Although transmission of drug-resistant tuberculosis in hospitals is well described,[7] a more complex web of interconnectedness in both health care and community settings is probably needed to support an epidemic of this scale. Further characterization of these networks is needed to design interventions in order to interrupt transmission.

Efforts to halt transmission have focused on health care settings, which typically have congregate wards and crowded clinics. Since the majority of study participants reported having been hospitalized, established interventions such as redesigning health care facilities, implementing infection-control programs, and providing outpatient treatment remain important considerations in designing a comprehensive strategy.[35–39] Methods for controlling transmission in community settings are less well studied. Since nearly half the epidemiologic links in our study occurred in households, interventions that decrease transmission in community settings are needed. Early identification of patients with drug-resistant tuberculosis, screening of household contacts, and universal drug-susceptibility testing for all patients who are suspected of having tuberculosis are recommended.[40,41]

Another finding from our study was the large pool of 2901 contacts who were exposed to XDR tuberculosis. The number of contacts per index case is consistent with the numbers in other contact-tracing studies in which nearly half the contacts became infected with tuberculosis.[29,41,42] If some of the contacts in this study became infected with XDR tuberculosis, a reservoir of latent XDR tuberculosis infection would be created, and this reservoir would further complicate control efforts. Without preventive therapy for latent XDR tuberculosis infection, these persons are at risk for reactivating and continuing to expand the epidemic of XDR tuberculosis.

Several limitations may have affected our estimates of transmission. Because of the large case numbers, we were not able to enroll all the patients with a diagnosis of XDR tuberculosis during the study period. In addition, because of limited use of culture and drug-susceptibility testing, many patients with XDR tuberculosis may not have been identified. The proportion of cases arising from transmission is therefore a minimal estimate because participants may have been misclassified as having unique genotypes if their source case did not receive a diagnosis or was not enrolled. The number of transmission links is also probably an underestimate, since unenrolled patients may have had linkages with our study participants. Nevertheless, our finding that 30% of the participants formed an epidemiologic cluster is striking.

Furthermore, since no reference standard exists for identifying transmission, we used a conservative case definition such that anyone who had received previous treatment for MDR tuberculosis was classified as having XDR tuberculosis that developed through acquired resistance. This definition may have resulted in misclassification, however, because persons who had MDR tuberculosis previously can be superinfected with XDR tuberculosis strains, and therefore XDR tuberculosis would have developed through transmission.[43]

Finally, we used a medical-record review to determine previous treatment for MDR tuberculosis. This approach may have resulted in an incomplete capture of antibiotic exposure for indications other than tuberculosis at hospitals or clinics that were not covered in our review. Despite the potential pitfalls of medical-record review, the results of genotyping and whole-genome sequencing in this study provide further evidence supporting the study findings.

The epidemic of drug-resistant tuberculosis is increasingly recognized as a threat to global health, given the limited treatment options and high mortality. The lack of effective preventive therapy for contacts of persons with XDR tuberculosis further underscores the need to control the current epidemic. We have shown that transmission was the major driver of the epidemic of XDR tuberculosis in KwaZulu-Natal during the study period. As the global tuberculosis community mobilizes around the goal of no new tuberculosis infections, the age-old approach of turning off the tap by stopping transmission is all the more critical for halting epidemics of drug-resistant tuberculosis.[44]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by grants from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH) (R01AI089349 and R01AI087465); NIH career development awards and training grants (K24AI114444, to Dr. Gandhi; K23AI083088, to Dr. Brust; and T32 HL116271, to Dr. Auld); and grants from the Emory University Center for AIDS Research (P30AI050409), the Albert Einstein College of Medicine Center for AIDS Research (P30AI051519), and the Albert Einstein College of Medicine Institute for Clinical and Translational Research (UL1 TR001073).

We thank the study team at the University of KwaZulu-Natal for their efforts in data collection, record abstraction, participant recruitment, and interviews; Darius McDaniel, Jonathan Smith, and Kristen Bratton for their contributions to data cleaning and analysis; Jennifer Lim, Shama Ahuja, and Roxana Rustomjee for early work in study design and implementation; Richard Rothenberg for contributions to network analysis; and the participants and their families.

References

1. Geneva: World Health Organization; 2015. Global tuberculosis report.
2. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014; 383:1230–1239. [PubMed: 24439237]
3. Liu CH, Li L, Chen Z, et al. Characteristics and treatment outcomes of patients with MDR and XDR tuberculosis in a TB referral hospital in Beijing: a 13-year experience. PLoS One. 2011; 6(4):e19399. [PubMed: 21559362]

4. Shah NS, Pratt R, Armstrong L, Robison V, Castro KG, Cegielski JP. Extensively drug-resistant tuberculosis in the United States, 1993–2007. JAMA. 2008; 300:2153–2160. [PubMed: 19001626]
5. Falzon D, Gandhi N, Migliori GB, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J. 2013; 42:156–168. [PubMed: 23100499]
6. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006; 368:1575–1580. [PubMed: 17084757]
7. Wells CD, Cegielski JP, Nelson LJ, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis. 2007; 196(Suppl 1):S86–S107. [PubMed: 17624830]
8. Moro ML, Gori A, Errante I, et al. An outbreak of multidrug-resistant tuberculosis involving HIV-infected patients of two hospitals in Milan, Italy. AIDS. 1998; 12:1095–1102. [PubMed: 9662207]
9. Ritacco V, Di Lonardo M, Reniero A, et al. Nosocomial spread of human immunodeficiency virus-related multidrugresistant tuberculosis in Buenos Aires. J Infect Dis. 1997; 176:637–642. [PubMed: 9291309]
10. Gelmanova IY, Keshavjee S, Golub chikova VT, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bull World Health Organ. 2007; 85:703–711. [PubMed: 18026627]
11. Pearson ML, Jereb JA, Frieden TR, et al. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis: a risk to patients and health care workers. Ann Intern Med. 1992; 117:191–196. [PubMed: 1352093]
12. Annual tuberculosis report for South Africa, 2012: research, information, monitoring, evaluation and surveillance. Pretoria: National TB Control and Management Cluster, Department of Health, Republic of South Africa. 2016
13. Shisana, O., Rehle, T., Simbayi, L., et al. South African national HIV prevalence, incidence and behavior survey. Cape Town, South Africa: HSRC Press; 2014.
14. Ndjecka N. Multi-drug resistant tuberculosis: strategic overview on MDR-TB care in South Africa. Pretoria: Department of Health, Republic of South Africa. 2014
15. Cook VJ, Sun SJ, Tapia J, et al. Transmission network analysis in tuberculosis contact investigations. J Infect Dis. 2007; 196:1517–1527. [PubMed: 18008232]
16. Clinical policies and protocols. 4th. New York: Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene; 2008.
17. Gandhi NR, Weissman D, Moodley P, et al. Nosocomial transmission of extensively drug-resistant tuberculosis in a rural hospital in South Africa. J Infect Dis. 2013; 207:9–17. [PubMed: 23166374]
18. Plus R: a suite of publicly available software programs for collecting and processing cancer registry data. Atlanta: National Center for Chronic Disease Prevention and Health Promotion; 2015.
19. Borgatti, SP., Everett, MG., Freeman, LC. Ucinet 6 for Windows: software for social network analysis. Harvard, MA: Analytic Technologies; 2002.
20. Shah NS, Wright A, Bai G-H, et al. Worldwide emergence of extensively drug-resistant tuberculosis. Emerg Infect Dis. 2007; 13:380–387. [PubMed: 17552090]
21. World TB Day — March 24, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:273. [PubMed: 27010173]
22. Farley JE, Tudor C, Mphahlele M, et al. A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa. Int J Tuberc Lung Dis. 2012; 16:82–89. [PubMed: 22236851]
23. Tudor C, Van der Walt M, Hill MN, Farley JE. Occupational health policies and practices related to tuberculosis in health care workers in KwaZulu-Natal, South Africa. Public Health Action. 2013; 3:141–145. [PubMed: 26393017]
24. Walker TM, Lalor MK, Broda A, et al. Assessment of Mycobacterium tuberculosis transmission in Oxfordshire, UK, 2007–12, with whole pathogen genome sequences: an observational study. Lancet Respir Med. 2014; 2:285–292. [PubMed: 24717625]
25. Guerra-Assunção JA, Crampin AC, Houben RM, et al. Large-scale whole genome sequencing of M. tuberculosis provides insights into transmission in a high prevalence area. Elife. 2015; 4:4.

26. Bryant JM, Schürch AC, van Deutekom H, et al. Inferring patient to patient transmission of Mycobacterium tuberculosis from whole genome sequencing data. BMC Infect Dis. 2013; 13:110. [PubMed: 23446317]
27. Glynn JR, Guerra-Assunção JA, Houben RM, et al. Whole genome sequencing shows a low proportion of tuberculosis disease is attributable to known close contacts in rural Malawi. PLoS One. 2015; 10(7):e0132840. [PubMed: 26181760]
28. Marais BJ, Mlambo CK, Rastogi N, et al. Epidemic spread of multidrug-resistant tuberculosis in Johannesburg, South Africa. J Clin Microbiol. 2013; 51:1818–1825. [PubMed: 23554196]
29. Becerra MC, Appleton SC, Franke MF, et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. Lancet. 2011; 377:147–152. [PubMed: 21145581]
30. Devaux I, Kremer K, Heersma H, Van Soolingen D. Clusters of multidrug-resistant Mycobacterium tuberculosis cases, Europe. Emerg Infect Dis. 2009; 15:1052–1060. [PubMed: 19624920]
31. Zhao Y, Xu S, Wang L, et al. National survey of drug-resistant tuberculosis in China. N Engl J Med. 2012; 366:2161–2170. [PubMed: 22670902]
32. Yang C, Shen X, Peng Y, et al. Transmission of Mycobacterium tuberculosis in China: a population-based molecular epidemiologic study. Clin Infect Dis. 2015; 61:219–227. [PubMed: 25829000]
33. Li X, Zhang Y, Shen X, et al. Transmission of drug-resistant tuberculosis among treated patients in Shanghai, China. J Infect Dis. 2007; 195:864–869. [PubMed: 17299717]
34. Said HM, Kock MM, Ismail NA, et al. Molecular characterization and second-line antituberculosis drug resistance patterns of multidrug-resistant Mycobacterium tuberculosis isolates from the northern region of South Africa. J Clin Microbiol. 2012; 50:2857–2862. [PubMed: 22649019]
35. Basu S, Andrews JR, Poolman EM, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. Lancet. 2007; 370:1500–1507. [PubMed: 17964351]
36. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City — turning the tide. N Engl J Med. 1995; 333:229–233. [PubMed: 7791840]
37. Barrera E, Livchits V, Nardell E. F-A-S-T: a refocused, intensified, administrative tuberculosis transmission control strategy. Int J Tuberc Lung Dis. 2015; 19:381–384. [PubMed: 25859991]
38. Loveday M, Wallengren K, Brust J, et al. Community-based care vs. centralised hospitalisation for MDR-TB patients, KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis. 2015; 19:163–171. [PubMed: 25574914]
39. Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med. 2003; 348:119–128. [PubMed: 12519922]
40. Theron G, Zijenah L, Chanda D, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. Lancet. 2014; 383:424–435. [PubMed: 24176144]
41. Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis. 2014; 58:381–391. [PubMed: 24065336]
42. Grandjean L, Gilman RH, Martin L, et al. Transmission of multidrug-resistant and drug-susceptible tuberculosis within households: a prospective cohort study. PLoS Med. 2015; 12(6):e1001843. [PubMed: 26103620]
43. Andrews JR, Gandhi NR, Moodley P, et al. Exogenous reinfection as a cause of multidrug-resistant and extensively drug-resistant tuberculosis in rural South Africa. J Infect Dis. 2008; 198:1582–1589. [PubMed: 18847372]
44. Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. Lancet. 2015; 386:2334–2343. [PubMed: 26515675]

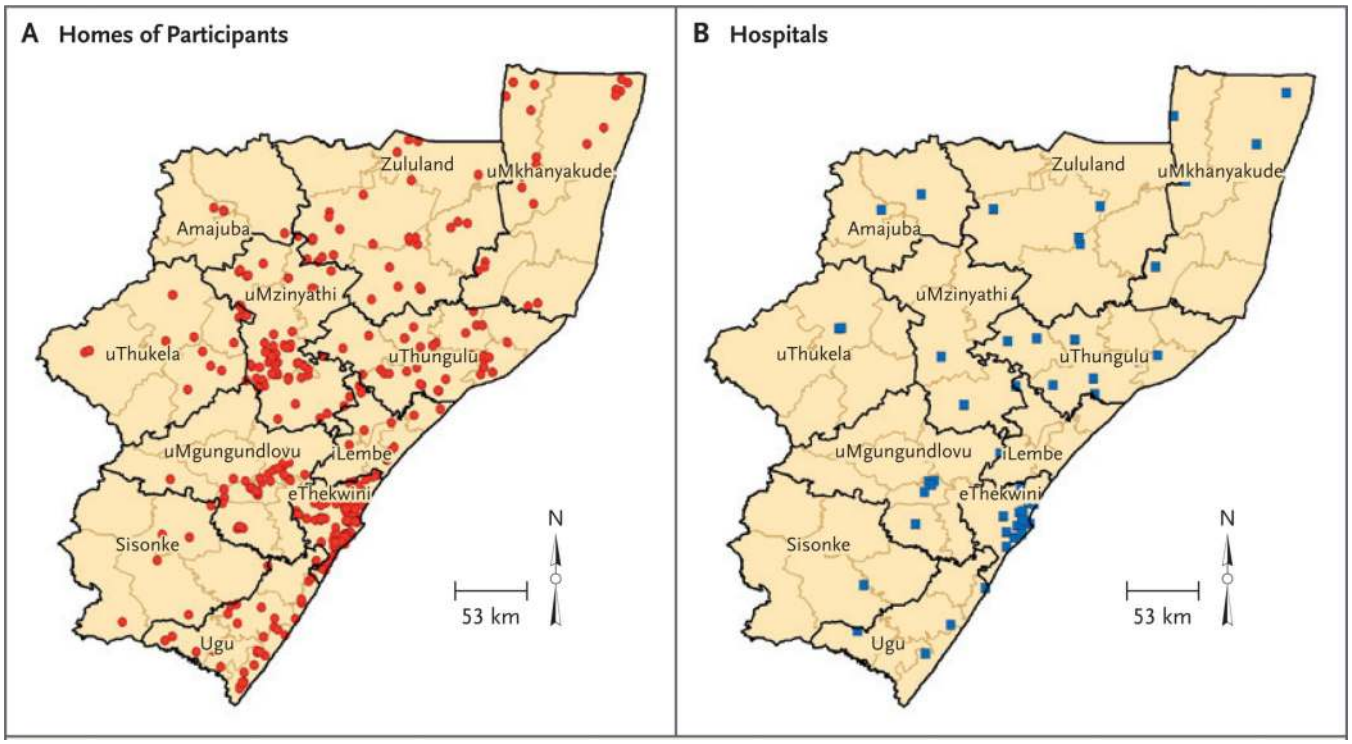

Figure 1. Geospatial Coordinates of Participants with Extensively Drug-Resistant (XDR) Tuberculosis in KwaZulu-Natal Province, South Africa

Panel A shows the homes (red dots) of all 404 enrolled participants. Panel B shows the 53 hospitals (blue squares) where the participants were admitted before or after XDR tuberculosis was diagnosed.

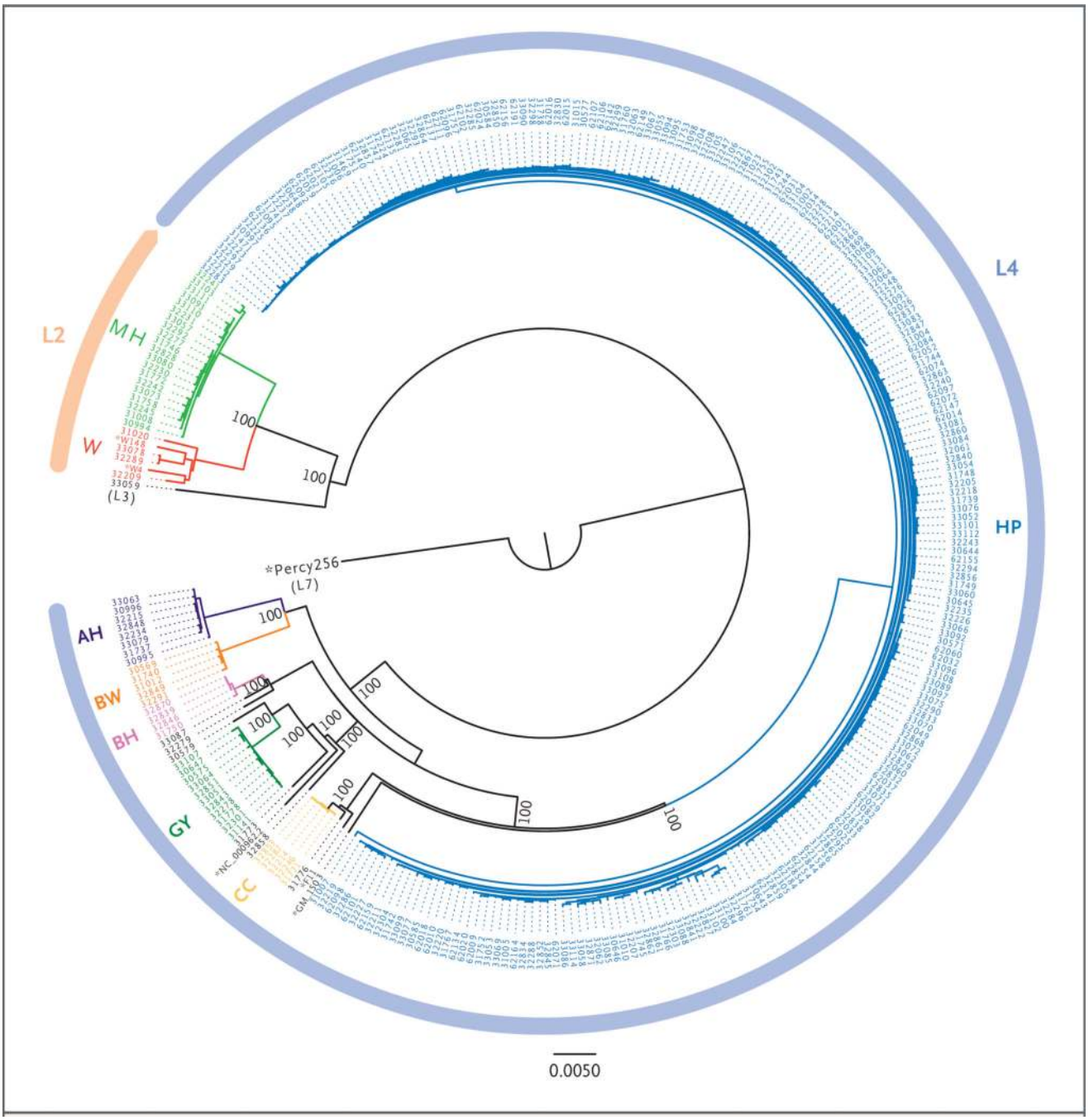

Figure 2. Single-Nucleotide Polymorphism (SNP)–Based Maximum Likelihood Phylogenetic Tree

Isolates are labeled according to study identification number and color coded according to restriction-fragment– length polymorphism (RFLP) group. Single-isolate RFLP groups are shown in black. The tree is rooted to the lineage 7 isolate Percy256. L2 denotes lineage 2, and L4 lineage 4. The other abbreviations (MH, W, AH, BW, BH, GY, CC, and HP) denote common RFLP patterns seen between isolates. The letters were assigned according to the first time that a particular RFLP pattern was seen (often many years before the current study). The blue circular band shows that all the isolates on the branches on the tree below it

are from lineage 4. The orange band shows that the isolates under it belong to lineage 2. At the center of the circular tree, one large branch separates all the isolates below the orange band from those below the blue band. All internal nodes separating RFLP groups are supported by 100 of 100 bootstrap replicates. Publicly available sequences (not sequenced for this study) are marked with asterisks. The scale bar indicates the maximum-likelihood estimate of the number of substitutions per site.

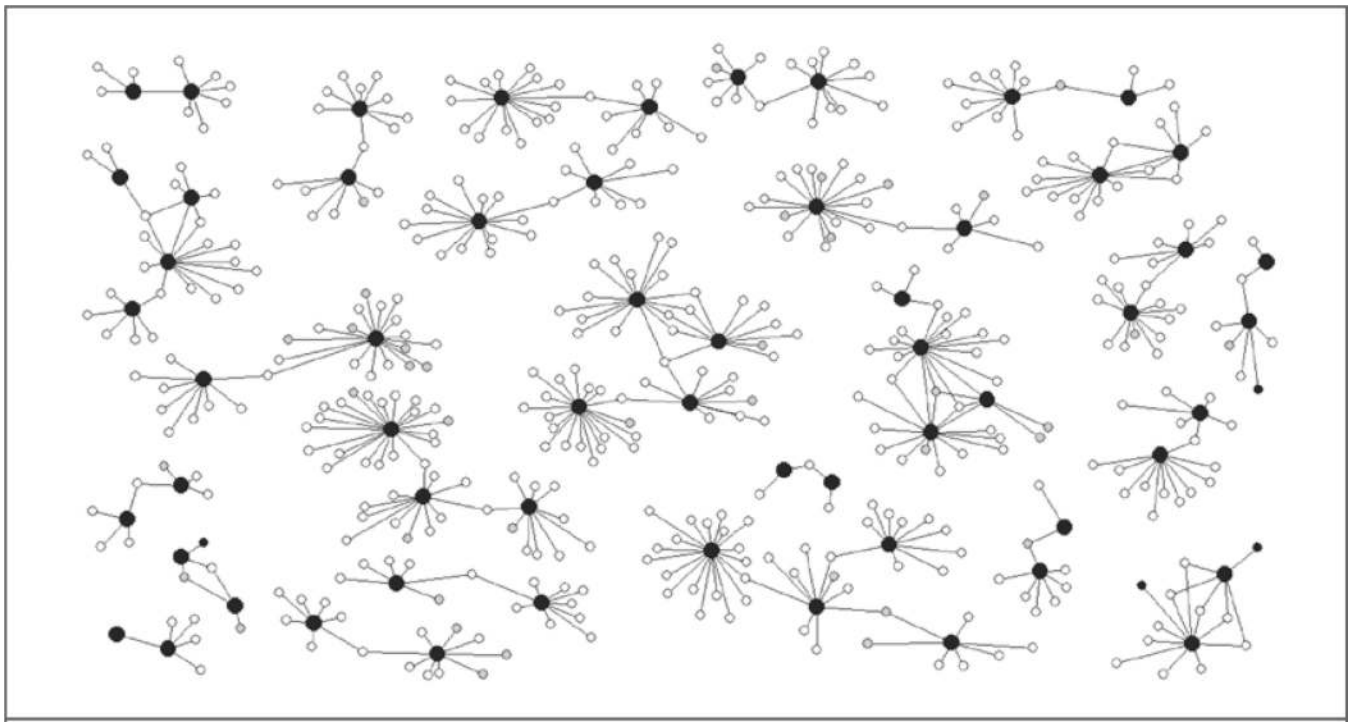

Figure 3. Social Networks in Homes and Communities, Derived from Name-Based Person-to-Person Links

A social network of 59 participants with direct person-to-person links is shown. Large black circles indicate study participants. Small circles indicate 450 close contacts named by participants. Lines between two large circles indicate 2 study participants who named each other as a close contact. Lines between a large circle and a small circle show contacts named by each participant. Contacts' circles are shaded according to their history of tuberculosis, as reported by the study participant (white denotes no previous active tuberculosis, gray previous active tuberculosis, and black previous XDR tuberculosis). Additional details are provided in Figure S3A in the Supplementary Appendix.

Table 1

Baseline Characteristics of the Participants with Extensively Drug-Resistant Tuberculosis in KwaZulu-Natal Province, South Africa, According to a Clinical Case Definition of Acquired or Transmitted Resistance.*

Characteristic	All Participants (N = 404)	Acquired Resistance (N = 124)	Transmitted Resistance (N = 280)†	P Value‡
Demographic				
Female sex — no. (%)	234 (58)	67 (54)	167 (60)	0.29
Age				
Median (IQR) — yr	34 (28–43)	33 (29–39)	34 (27–44)	0.40
Age group — no. (%)				0.06
0–15 yr	16 (4)	2 (2)	14 (5)	
16–34 yr	207 (51)	72 (58)	135 (48)	
35–54 yr	150 (37)	45 (36)	105 (38)	
≥55 yr	31 (8)	5 (4)	26 (9)	
Rural residence — no. (%)	204 (50)	62 (50)	142 (51)	0.66
Monthly household income — South African rand§				0.01
<R500	139 (34)	32 (26)	107 (38)	
R500–R2,500	186 (46)	58 (47)	128 (46)	
>R2,500	79 (20)	34 (27)	45 (16)	
Children in household				
Patients who reported children residing in household — no. (%)	303 (75)	95 (77)	208 (74)	0.62
Median no. of children/household (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.58
Occupation — no. (%)				
Health care worker	24 (6)	8 (6)	16 (6)	0.77
Mine worker	5 (1)	2 (2)	3 (1)	0.65
Clinical				
Current smoker — no. (%)	39 (10)	15 (12)	24 (9)	0.21
Diabetes — no. (%)	23 (6)	4 (3)	19 (7)	0.15
Positive for HIV infection				
Patients with HIV infection — no. (%)	311 (77)	97 (78)	214 (76)	0.69
Median CD4+ T-cell count (IQR) — cells/mm^3	340 (117–431)	306 (135–433)	354 (111–430)	0.46
Undetectable viral load — no./total no. (%)	155/311 (50)	48 (39)	107 (38)	0.92
Use of antiretroviral therapy at study enrollment — no./total no. (%)	236/311 (76)	78 (63)	158 (56)	0.01
Cough				
Patients with cough — no. (%)	333 (82)	107 (86)	226 (81)	0.17
Median duration of cough (IQR) — wk	8 (4–12)	10 (5–12)	9 (4–13)	0.12
Chest radiography — no. (%)				
Cavitation	70 (17)	27 (22)	43 (15)	0.11

Characteristic	All Participants (N = 404)	Acquired Resistance (N = 124)	Transmitted Resistance (N = 280)†	P Value‡
Bilateral disease	112 (28)	45 (36)	67 (24)	0.01
Sputum smear positive for acid-fast bacilli — no. (%)	270 (67)	94 (76)	176 (63)	0.04
Hospitalization history				
Any — no. (%)	298 (74)	101 (81)	197 (70)	0.02
Median no. (range)	1 (1–5)	1 (1– 5)	1 (1–3)	0.14
≥2 hospitalizations — no./total no. (%)	86/298 (29)	35/101 (35)	51/197 (26)	0.11
Previous treatment for tuberculosis				
Any — no. (%)	291 (72)	124 (100)	167 (60)	<0.001
Drug-susceptible tuberculosis				
Treatment — no. (%)	260 (64)	93 (75)	167 (60)	0.003
Median duration of treatment (IQR) — mo	6 (6–12)	6 (6–12)	6 (6–12)	0.44
Multidrug-resistant tuberculosis				
Treatment — no. (%)	124 (31)	NA	NA	NA
Median duration of treatment (IQR) — mo	6 (4–12)	NA	NA	
Outcome of previous treatment — no./total no. (%)¶				
Cure or completed treatment	7/119 (6)	NA	NA	
Treatment failure	100/119 (84)	NA	NA	
Loss to follow-up or transferred	12/119 (10)	NA	NA	

*IQR denotes interquartile range.

†Previous treatment for tuberculosis precludes transmitted resistance, so some cells in this column are not applicable (NA).

‡P values were calculated with the use of the chi-square test, Fisher's exact test, and t-tests for the comparison of the acquired-resistance group with the transmitted-resistance group.

§During the study period, the currency conversion was approximately 1 U.S. dollar to 8.4 South African rand.

¶Treatment outcomes were available for 119 of the 124 participants (96%) who reported receiving previous treatment for MDR tuberculosis.