

ported by Fischer et al.² in a patient with mild myopathy.

The atherosclerotic lesion that we observed in this patient was unusual³ because the accumulated lipid was triglyceride rather than cholesterol, lipid-laden cells were distributed through all layers of the arterial wall, and the patient had normal plasma triglyceride levels. These phenotypes may result from the mutation in *ATGL*.⁴

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1. Haemmerle G, Lass A, Zimmermann R, et al. Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. *Science* 2006;312:734-7.
2. Fischer J, Lefèvre C, Morava E, et al. The gene encoding adipose triglyceride lipase (PNPLA2) is mutated in neutral lipid storage disease with myopathy. *Nat Genet* 2007;39:28-30.
3. Ross R. Atherosclerosis — an inflammatory disease. *N Engl J Med* 1999;340:115-26.
4. Schweiger M, Schoiswohl G, Lass A, et al. The C-terminal region of human adipose triglyceride lipase affects enzyme activity and lipid droplet binding. *J Biol Chem* 2008;283:17211-20.

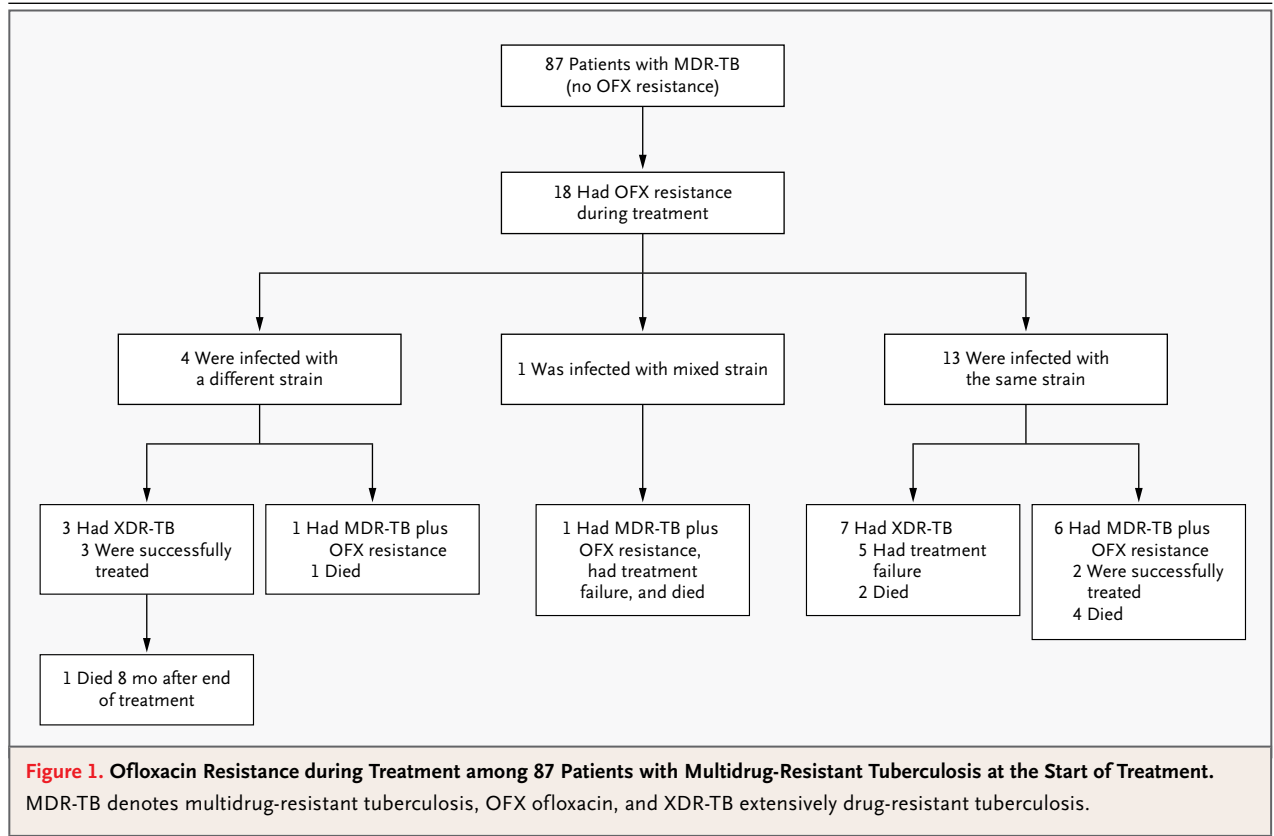
Emergence of Extensive Drug Resistance during Treatment for Multidrug-Resistant Tuberculosis

TO THE EDITOR: We report the development of fluoroquinolone-resistant tuberculosis and extensively drug-resistant tuberculosis during second-line treatment for multidrug-resistant tuberculosis in Karakalpakstan, Uzbekistan. Eighty-seven patients were treated with a regimen containing at least five drugs to which the infecting strain was presumed to be susceptible, according to recommendations from the World Health Organization.^{1,2} We performed drug-susceptibility testing and DNA fingerprinting on *Mycobacterium tuberculosis* isolates collected at baseline and during treatment.

None of the 87 patients had ofloxacin resistance at baseline, yet ofloxacin resistance developed during treatment in 18 patients (21%), and 10 patients (11%) were classified as having extensively drug-resistant tuberculosis.³ Only 5 (28%) of the 18 patients with ofloxacin resistance were successfully treated. Isolates from 13 patients had identical DNA fingerprints throughout treatment, probably reflecting the induction and amplification of ofloxacin resistance. A mixed infection, with two strains at baseline, was found in one patient, whereas the isolates obtained from four patients during treatment had DNA fingerprints that differed from those of the baseline isolates, indicating potential reinfection (Fig. 1).

Among the 13 patients with identical strains at baseline and during treatment, second-line resistance and a severe clinical condition at baseline were significantly associated with the development of ofloxacin resistance on univariate analysis ($P=0.002$ and $P=0.03$, respectively) (see the Supplementary Appendix, available with the full text of this letter at www.nejm.org). Both factors remained significantly associated with fluoroquinolone resistance in a multivariate model ($P=0.007$ and $P=0.03$, respectively). Interestingly, 9 of the 13 patients were infected with a multidrug-resistant tuberculosis clone that is highly prevalent in this region, suggesting a higher propensity of particular strains to acquire resistance. A reduction in population diversity caused by clonal expansion of particular multidrug-resistant strains also renders strain differentiation based on IS6110 fingerprints more difficult. Thus, some of the presumed amplification might represent reinfection with a fluoroquinolone-resistant variant of the same strain.

This study shows that exogenous reinfection with extensively drug-resistant *M. tuberculosis* strains may occur during second-line treatment of multidrug-resistant tuberculosis. The reinfecting strains from three patients showed DNA fingerprint patterns and resistance profiles that were identical to



those of *M. tuberculosis* strains obtained from patients who stayed in the same hospital during the same time. These data point to the risk of nosocomial transmission of extensively drug-resistant tuberculosis strains in high-incidence settings, even with implementation of infection-control measures such as ultraviolet germicidal irradiation, natural and artificial ventilation, and limitations on the number of patients per room.

The emergence of fluoroquinolone resistance and extensively drug-resistant tuberculosis during treatment of multidrug-resistant tuberculosis with currently recommended protocols, under well-controlled conditions, has significant implications for the scale-up of multidrug-resistant tuberculosis treatment internationally. With an estimated 489,000 new cases of multidrug-resistant tuberculosis emerging each year, the need to scale up treatment is undeniable.⁴ However, the risk of creating and transmitting highly resistant *M. tuberculosis* strains highlights the need to optimize treatment regimens and develop strategies for administering these regimens safely and effectively.⁵

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The Karakalpakstan MDR-TB treatment program is funded by Médecins Sans Frontières (Amsterdam). The National Reference Center for Mycobacteria, in Borstel, Germany, is supported by the German Ministry of Health.

1. Cox HS, Kalon S, Allamuratova S, et al. Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. *PLoS ONE* 2007;2(11):e1126.
2. Guidelines for the programmatic management of drug-resistant tuberculosis Geneva: World Health Organization, 2006. (Publication no. WHO/HTM/TB/2006.361.)

3. Migliori GB, Besozzi G, Girardi E, et al. Clinical and operational value of the extensively drug-resistant tuberculosis definition. *Eur Respir J* 2007;30:623-6.

4. Anti-tuberculosis drug resistance in the world. Report no. 4 Geneva: World Health Organization, 2008. (Publication no. WHO/HTM/TB/2008.394.)

5. Mitnick CD, Castro KG, Harrington M, Sacks LV, Burman W. Randomized trials to optimize treatment of multidrug-resistant tuberculosis. *PLoS Med* 2007;4(11):e292.

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