A complete list of authors is available with the full text of this letter at NEJM.org.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC) and other funding agencies.

Supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through the CDC under the terms of grant numbers GH001490 and GH002027.

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

This letter was published on July 22, 2019, at NEJM.org.

1. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med 2018;379:979-81.
2. Daly L. Simple SAS macros for the calculation of exact binomial and Poisson confidence limits. Comput Biol Med 1992;22:351-61.
3. Tandberg D. Improved confidence intervals for the difference between two proportions and number needed to treat (NNT), version 1. Albuquerque: University of New Mexico School of Medicine (https://www.cebm.net/wp-content/uploads/2014/04/Diff2PropCI49.xls).
4. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. N Engl J Med 2019;381:827-40.

DOI: 10.1056/NEJMc1908155

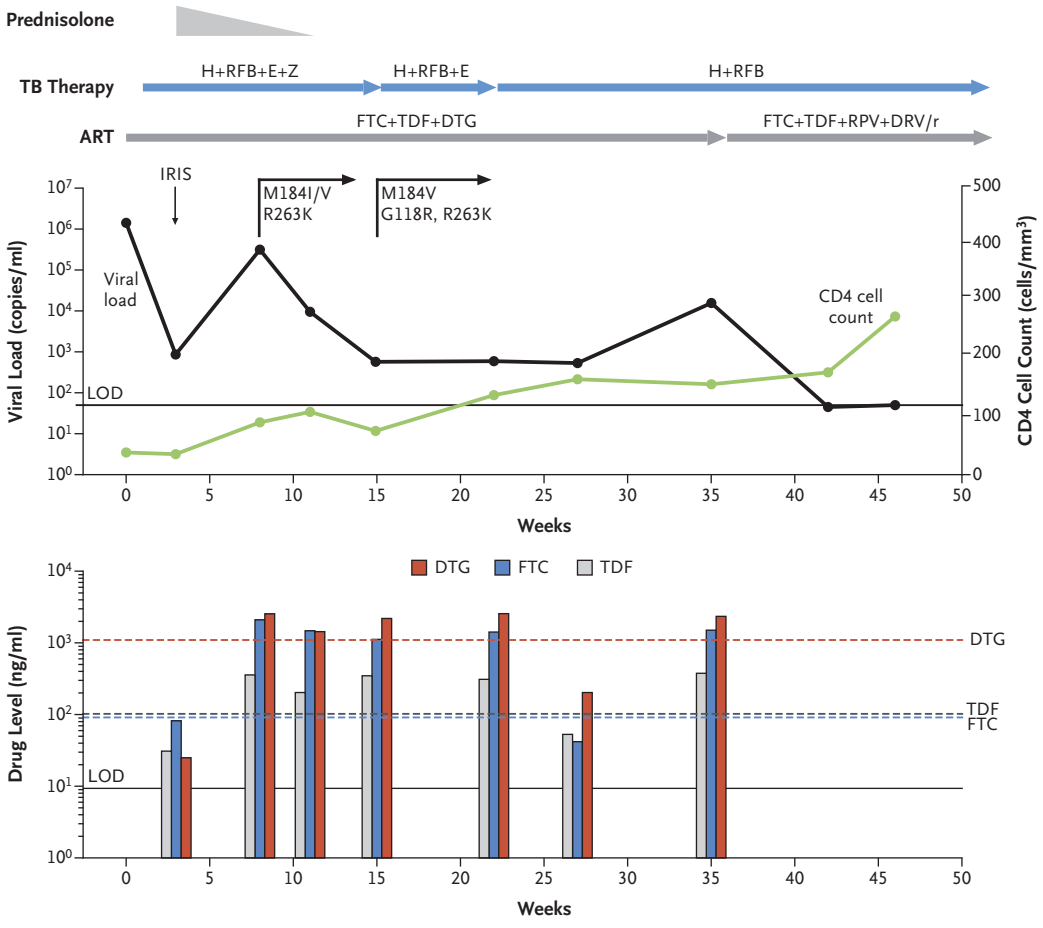
Failure of Dolutegravir First-Line ART with Selection of Virus Carrying R263K and G118R

TO THE EDITOR: The human immunodeficiency virus type 1 (HIV-1) integrase inhibitor dolutegravir is recommended in treatment guidelines as first-line therapy for HIV-1 infection and is characterized by high antiviral potency and a high genetic barrier to the emergence of resistance. Few cases of virologic failure of dolutegravir first-line therapy have been reported, but the relevance of resistance-associated mutations in these cases is unclear.[1,2] Here, we describe a case of virologic failure in an HIV-1–infected patient who had not previously received antiretroviral treatment (ART) and who was receiving emtricitabine, tenofovir disoproxil fumarate, and dolutegravir, with the emergence of the dolutegravir resistance-associated mutations R263K and G118R.

A 27-year-old man who has sex with men who was infected with HIV-1 subtype F was admitted to the hospital with advanced HIV-1 infection, a viral load of 1.4×10^6 copies per milliliter, a CD4 cell count of 22 per cubic millimeter, and *Mycobacterium tuberculosis* coinfection. Treatment with emtricitabine, tenofovir disoproxil fumarate, and dolutegravir was initiated, with a response indicated by a 3-log decline in viral load within the first 3 weeks of hospitalization and a slow recovery of the CD4 cell count. Disseminated tuberculosis, including tuberculous pericarditis, was diagnosed, and treatment with isoniazid, rifabutin, ethambutol, and pyrazinamide was initiated 1 week after the start of ART, supplemented with prednisolone when immune reconstitution inflammatory syndrome (IRIS) was diagnosed (Fig. 1A, and the Supplementary Appendix, available with the full text of this letter at NEJM.org).

After the patient was discharged from the hospital, his viral load increased to 311,894 copies per milliliter, which was initially interpreted as resulting from a problem with adherence. During subsequent therapy, the viral load decreased to approximately 500 copies per milliliter, but viral suppression below the limit of detection was not achieved. A resistance analysis conducted 8 months after therapy initiation revealed the emtricitabine resistance–associated mutation M184V and the dolutegravir resistance–associated mutations G118R and R263K. Retrospective resistance analyses showed that resistance-associated mutations were detected at baseline only at very low frequencies (<0.2%); however, R263K was present at a frequency of 64.1% by week 8, during the first viral rebound, and the G118R mutation was present at a frequency of 23.0% by week 15 (Fig. 1B). The mutations associated with dolutegravir resistance were detected at different frequencies by means of ultradeep sequencing, which indicated that evolution of distinct variants within the quasi-species was occurring, a finding consistent with the presence of distinct resistance pathways.[3] The ART drug levels were mostly adequate during treatment for tuberculosis. In line with the dolutegravir prescribing information and previous observations, the insufficient levels of dolutegravir at weeks 3 and 26 seemed not to be related to

A Viral Loads, CD4 Cell Counts, and Drug Levels



B Resistance Analysis

Mutation	Wk 0	Wk 3	Wk 8	Wk 11	Wk 15	Wk 22	Wk 27	Wk 35	Wk 36
					%				
M184V	0.17	0.22	85.8	95.6	98.1	98.6	ND	99.4	99.6
M184I	0.09	0.07	13.6	2.9	0.0	0.0	ND	0.0	0.0
G118R	0.01	0.00	0.0	4.0	23.0	0.0	0.0	29.7	45.2
R263K	0.00	0.00	64.1	82.9	69.8	99.4	99.2	69.2	30.4

drug interactions with rifabutin.[4] After switching combined ART to emtricitabine, tenofovir disoproxil fumarate, rilpivirine, and darunavir–ritonavir, stable viral suppression was achieved and therapy for tuberculosis was successfully completed.

Resistance to dolutegravir, even in patients who have not previously received ART, can occur and should be considered in the context of an inadequate response to ART. Risk factors like infection with a non-B subtype of HIV-1,[3] a high viral load and low CD4 cell count,[5] insufficient adherence to ART, and coinfections influencing drug levels may facilitate the selection of dolutegravir-resistant variants — in this case, variants carrying R263K and G118R.

Nadine Lübke, Ph.D.
Björn Jensen, M.D.
Falk Hüttig, M.D.
Torsten Feldt, M.D.
Andreas Walker, Ph.D.

Heinrich Heine University Hospital
Düsseldorf, Germany
nadine.luebke@med.uni-duesseldorf.de

Figure 1 (facing page). Clinical Course of First-Line Therapy Failure with a Dolutegravir-Containing Regimen.

Panel A shows human immunodeficiency virus type 1 (HIV-1) viral loads, CD4 cell counts, and drug levels in plasma. First-line antiretroviral treatment (ART) was initiated with emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), and dolutegravir (DTG) with a viral load greater than 10^6 copies per milliliter and a low CD4 cell count. CD4 cell counts and viral loads are shown in the top graph, and levels of the ART drugs are shown in the bottom graph. The mean reference trough levels (C_{MIN}) are indicated by the corresponding colored dashed lines (DTG, 1110 ng per milliliter; FTC, 90 ng per milliliter [range, 20 to 160]; TDF, 100 ng per milliliter [range, 20 to 180]). After a 3-log decrease in viral load within the first 3 weeks of treatment, the viral load had rebounded by week 8 and subsequently decreased to less than 1000 copies per milliliter by week 15; however, viral suppression to below the limit of detection (LOD) was not achieved. Tuberculosis treatment was started with isoniazid (H), rifabutin (RFB), ethambutol (E), and pyrazinamide (Z) 1 week after ART initiation, was reduced to isoniazid, rifabutin, and ethambutol in week 15, and finally continued with isoniazid and rifabutin from week 22 to the end of treatment, approximately 60 weeks after the start of therapy. Immune reconstitution inflammatory syndrome (IRIS) with severe pericardial effusion, diagnosed in week 3, was managed by emergency pericardiocentesis and treatment with 60 mg of prednisolone that was gradually tapered over 8 weeks. Resistance analysis revealed resistance against FTC (M184V and M184I mutations) and DTG (R263K) in week 8. In addition, the DTG-specific G118R mutation increased substantially in frequency by week 15. By week 35, the viral load had increased again, and ART was switched to FTC, TDF, rilpivirine (RPV), and ritonavir-boosted darunavir (DRV/r); the response to this regimen was adequate (i.e., viral load decreased to below the limit of detection of 50 copies per milliliter). Panel B shows the results of the resistance analysis of target genes by next-generation sequencing. HIV resistance analysis was performed as part of the RESINA (Primary Drug Resistance in Treatment Naive HIV-Infected Patients) study before ART initiation (week 0) and at the time of virologic failure, when viral loads increased after an initial decline, and was performed retrospectively for the analysis of resistance evolution for all available plasma samples. The first detection of HIV-1 with resistance against TDF, FTC, or DTG is shown in red. All resistance analyses were performed by next-generation sequencing with Illumina MiSeq technology. ND denotes not determined.

Alexander Thielen, Ph.D.
Martin Däumer, M.Sc.

Institute of Immunology and Genetics
Kaiserslautern, Germany

Martin Obermeier, M.D.

Medical Center for Infectious Diseases
Berlin, Germany

Rolf Kaiser, Ph.D.
Elena Knops, Ph.D.
Eva Heger, Ph.D.
Saleta Sierra, Ph.D.

University Hospital Cologne
Cologne, Germany

Mark Oette, M.D.

Augustinerinnen Hospital
Cologne, Germany

Thomas Lengauer, Ph.D.

MPI for Informatics
Saarbrücken, Germany

Jörg Timm, M.D.
Dieter Häussinger, M.D.

Heinrich Heine University Hospital
Düsseldorf, Germany

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

1. Fulcher JA, Du Y, Zhang TH, Sun R, Landovitz RJ. Emergence of integrase resistance mutations during initial therapy containing dolutegravir. Clin Infect Dis 2018;67:791-4.
2. Taiwo BO, Zheng L, Stefanescu A, et al. ACTG A5353: a pilot study of dolutegravir plus lamivudine for initial treatment of human immunodeficiency virus-1 (HIV-1)-infected participants with HIV-1 RNA <500000 copies/mL. Clin Infect Dis 2018;66:1689-97.
3. Quashie PK, Oliviera M, Veres T, et al. Differential effects of the G118R, H51Y, and E138K resistance substitutions in different subtypes of HIV integrase. J Virol 2015;89:3163-75.
4. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr 2013;62:21-7.
5. Lepik KJ, Harrigan PR, Yip B, et al. Emergent drug resistance with integrase strand transfer inhibitor-based regimens. AIDS 2017;31:1425-34.

DOI: 10.1056/NEJMc1806554

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere.

Letters accepted for publication will appear in print, on our website at NEJM.org, or both.

Please note the following:

- **Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article.**
- **Letters not related to a *Journal* article must not exceed 400 words.**
- **A letter can have no more than five references and one figure or table.**