

HIV Drug Resistance Is Declining Over Time

Resistance to multiple classes of antiretroviral is now uncommon but is seen more often in archived viral DNA from older people.

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Overall rates of [HIV drug resistance](#) declined by nearly 17% between 2018 and 2024, according to a large analysis from Quest Diagnostics published in [Open Forum Infectious Diseases](#). The researchers assessed the prevalence of mutations that confer resistance to nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors and integrase inhibitors.

“Prevalence of NRTI and NNRTI resistance has declined, consistent with increased use of regimens with higher resistance barriers, improved tolerability and more convenient dosing,” the study authors concluded. “Continued advances in antiretroviral therapy efficacy, durability and tolerability may lead to increased rates of virologic suppression and further reduce the incidence of archived resistance mutations in proviral DNA.”

When antiretroviral medications are used incorrectly or inconsistently, HIV can continue to replicate and develop resistance to the drugs, reducing their effectiveness and compromising future treatment options. With the advent of modern antiretrovirals that are easier to take and less prone to resistance, this problem is less common than it was in the early years of combination therapy, but it remains a concern.

Ron Kagan, PhD, of Quest Diagnostics in San Juan Capistrano, California, and colleagues looked at trends in drug-resistance mutations based on genetic sequences from more than 90,000 blood tests collected between January 2018 and May 2024. More than 75% of specimens were from men. The researchers analyzed the annual prevalence of mutations with a Stanford HIV Drug Resistance Database score of 30 or higher for NRTIs, NNRTIs, protease inhibitors and integrase inhibitors.

Overall, the prevalence of drug resistance mutations declined in both HIV RNA and HIV DNA sequences. HIV RNA reflects current viral replication while proviral DNA—viral genetic material integrated into CD4 cells—reflects “archived” inactive virus. Resistance mutations in RNA fell from about 30% in 2018 to about 25% in 2024. DNA results were similar using a 10% cutoff for minority viral variants, rising to 38% and 29%, respectively, when using a 20% cutoff. While both single-

and dual-class NRTI and NNRTI resistance fell over time, it remained higher in DNA compared with RNA sequences, indicating a history of prior resistance.

NRTIs

The NRTI resistance mutations known as K65R/N, which confers resistance to tenofovir, and M184V/I, linked to reduced activity of lamivudine and emtricitabine, both declined over time. Combination pills containing tenofovir disoproxil fumarate (including Truvada and Atripla) and tenofovir alafenamide (including Descovy and Biktarvy) are widely used for HIV treatment and pre-exposure prophylaxis (PrEP). Lamivudine or emtricitabine are included in most combination regimens.

In their discussion, the researchers suggested that the decrease in K65R/N and M184V/I mutations may reflect increasing use of tenofovir, lamivudine and emtricitabine in combination with integrase inhibitors, which makes for more potent regimens. Fortunately, the presence of M184V/I may not seriously compromise treatment effectiveness, and resistance mutations can disappear over time.

One recent retrospective study, [published in the journal AIDS](#), looked at 338 treatment-experienced people in France, 13% of whom had the M184V/I mutation. Among those who switched to the widely used “TLD” (tenofovir disoproxil fumarate/lamivudine/dolutegravir) regimen, efficacy was statistically similar for those with and without M184V/I. The rate of virological failure at six months was 17.8% versus 14.0%, respectively, for people with and without the mutation, while the likelihood of viral blips was 6.7% and 2.4%, respectively; neither difference was statistically significant.

Another study, published in [Clinical Infectious Diseases](#), included 121 people on treatment with viral suppression who had suspected or confirmed prior resistance to lamivudine; however, only one in five currently had detectable M184V/I in proviral DNA. After excluding these individuals, more than 90% of the remainder who switched to a simplified two-drug maintenance regimen of dolutegravir and lamivudine (sold as Dovato) maintained an undetectable viral load.

Other Drug Classes

Mutations conferring resistance to the NNRTI rilpivirine remained low, with a prevalence of 6.3% in HIV RNA and 10.2% in HIV DNA in 2024. Rilpivirine is sold alone as Edurant and is a component of the Complera, Juluca and Odefsey single-tablet regimens and the long-acting injectable regimen Cabenuva. The prevalence of mutations associated with resistance to doravirine (sold alone as Pifeltro and a component of the Delstrigo combination pill) was 2% in RNA and 2.9% in DNA in 2024. The signature mutation that confers resistance to the older NNRTIs efavirenz and nevirapine, known as K103N, continued to decline but remained above 10%.

The prevalence of major protease inhibitor resistance mutations in HIV DNA sequences declined from 5.3% in 2018 to 2.1% in 2024, coinciding with declining use of this drug class, and remained

below 3% in HIV RNA sequences.

The prevalence of resistance to integrase inhibitors also declined overall, but the R263K mutation, associated with resistance to dolutegravir (sold alone as Tivicay and part of the Dovato, Juluca and Triumeq single-tablet regimens) and cross-resistance to bictegravir (in Biktarvy) and cabotegravir (in Cabenuva for HIV treatment and Apretude for PrEP), showed an increase over time. “Increases in the prevalence of R263K may affect future [integrase inhibitor] treatment and PrEP options and should continue to be monitored,” the authors wrote.

Multiclass Resistance

Developing resistance to more than one class of antiretrovirals makes it harder to build an effective regimen using remaining drug classes. Between 2018 and 2024, combined NRTI and NNRTI resistance declined from 6.1% to 3.5% in HIV RNA and from 12.1% to 7.8% in HIV DNA. The prevalence of dual NRTI and integrase resistance also declined. By 2024, just 4.7% of HIV RNA sequences (down from 8.7% in 2018) and 8.5% of DNA sequences (down from 13.1%) harbored dual-class resistance to a NRTI plus either a NNRTI or an integrase inhibitor.

However, the researchers noted, there was a significant difference by age. Dual-class and triple-class resistance were more common among older people, who might have tried many drugs in suboptimal combinations over the years. Dual NRTI and NNRTI resistance was detected in just 3.8% of people ages 18 to 39, rising to 14.1% among those ages 60 or older. Triple-class resistance including protease mutations was below 0.5% in HIV RNA sequences from younger adults but rose to 3.9% in HIV DNA from older adults, reflecting archived virus.

“As people with HIV in younger age groups started therapy on contemporary regimens with higher barriers to resistance and better tolerability than first-generation NRTI-, NNRTI- and protease inhibitor-based regimens, future resistance rates as this cohort ages may remain lower,” the authors wrote.

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