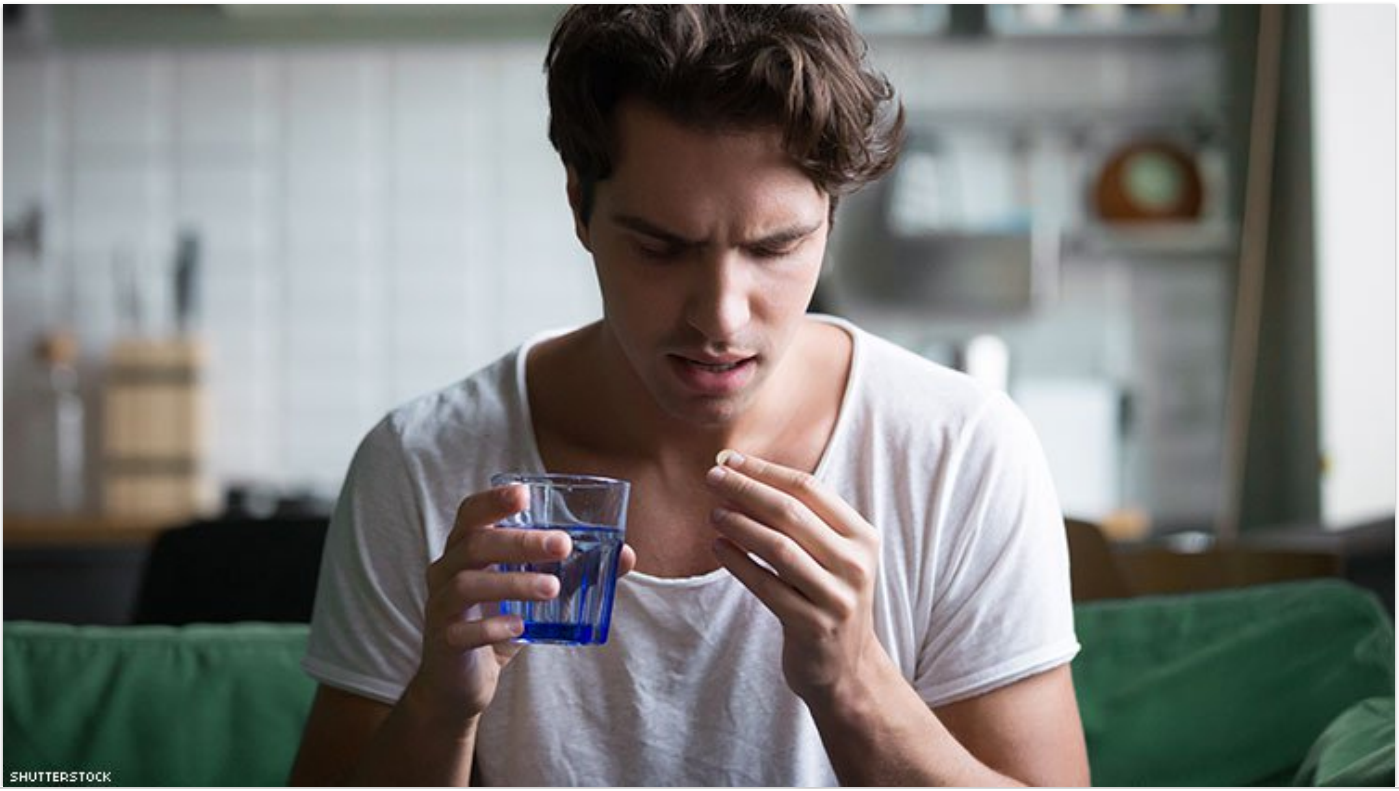
HIV Drugs With Fewer Side Effects Need More FDA Support



New medicines providing a better quality of life should always be top priority when asking for federal support.

By Jeannie Wraight

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While modern medicines have made HIV a chronic manageable condition, serious side effects from antiretrovirals are still greatly affecting the quality of life for many HIV-positive people.

There are significantly lower side effects with newer drugs than in ARVs approved in the

The future of HIV drugs with fewer side effects is drawing near, but is it possible for drug makers to speed it along?

In 2018, six HIV antivirals were approved by the FDA. Four of the six "new" therapies (fixed dose combinations of previously approved drugs) satisfy the need for viral suppression and once-a-day dosing. However, these therapies are linked to many adverse events and even life-threatening serious adverse events, and as such, do not fulfill the criteria for limiting side effects.

Side effects, both bothersome and serious, can be temporary or have long lasting impacts. These include diarrhea, Lipodystrophy, fatigue, bone pain/disease, nausea, and depression. Drugs approved in 2018 — like Symtuza, Delstrigo and Ibalizumab — as is the case with many other ARVs, are also linked to serious complications such as cardiovascular disease, diabetes, liver, kidney and pancreas disease, and immune reconstitution inflammatory syndrome (IRIS).

As long as HIV medications are required to be taken indefinitely and, from a public health standpoint, to limit new incidents of HIV, special regulatory attention should be given to ensure adverse effects and serious adverse effects are limited — and not impacting adherence in taking them.

Priority in publicly sponsored clinical trials and NIH funded grants should be given to therapeutics that are specifically designed with attention to a reduction in side effects. This would provide pharmaceutical and biotechnology companies developing ARVs a strong incentive to invest the R&D dollars, time, and effort in doing so.

Some drugs by their very nature are thought to produce less toxicities and fewer side effects. ABX464, a Rev Inhibitor currently in Phase II trials; BIT225, a VPU inhibitor also in Phase II; and Baricitinib, a Jax inhibitor being studied as a functional cure, all demonstrate superior toxicity profiles to current regimens. The fewer side effects with more convenient dosing (like once-a-day or long-acting) are considered more "superior."

Another new drug in early development thought to have low toxicity is DDX3 RNA Helicase inhibitors being developed by a European pharmaceutical company, First Health Pharmaceuticals. DDX3 Inhibitors are being considered for a list of infectious diseases like HIV, hepatitis C, ebola, dengue, and Zika, as well as for several forms of HIV-related

DDX3 Inhibitors have been shown to be active against all strains of HIV. They work by targeting DDX3 RNA Helicase, a human protein that is hijacked by HIV and essential for the replication of the virus as well as the assembly of HIV to enable it to replicate. In addition to low toxicity, a major advantage of targeting a human protein verses targeting HIV itself is that resistance cannot occur as with current therapies, where HIV can mutate and overcome attack. This lack of resistance has been observed during in vitro studies where there was no selection of mutated resistant strains long after treatment at active doses.

Although drug resistance has decreased substantially, the rate of drug resistance (especially pre- treatment drug resistance) is increasing steadily, particularly in low- and middle-income countries.

Research shows that in these countries, the rate of pre-treatment drug resistance has reached, or is exceeding, 10 percent. These rates have been reported to be increasing each year, with Southern Africa experiencing a 23 percent increase in annual risk of pre-treatment drug resistance, and an increase of approximately 36 percent in Eastern Africa.

The World Health Organization's Global Action Plan on HIV Drug Resistance 2017–2021 states: "The financial and human impact of HIV DR [drug resistance] across sub-Saharan Africa estimates that if levels of PDR are over 10% in the next 5 years, HIV drug resistance is predicted to be responsible for 424,937 additional AIDS deaths, over 302,000 new infections, and will result in costs of ART delivery of nearly 3 billion USD."

New drugs with reduced drug resistance and toxicity profiles should be a priority to quell the growing rate of pre-treatment drug resistance and better quality of life and drug adherence for those who suffer with persistent ARV side effects. Such drugs should be prioritized in the HIV pipeline when considered for federal support. Only when this becomes the standardized norm will we see more drugs developed from conception that possess these qualities.

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