First-in-class HIV drug enters phase 3 trials

New York–based Bristol-Myers Squibb (BMS) has moved a first-in-class HIV attachment inhibitor into phase 3 testing, after announcing positive results from a 48-week phase 2b study in February. BMS-663068 is the first drug to target the protein gp120 on the viral envelope to prevent initial attachment to the CD4 receptor. Because this small molecule works through a novel mechanism and targets a highly conserved area of the virus, it could be particularly useful in people with resistant HIV who have had many other treatments.

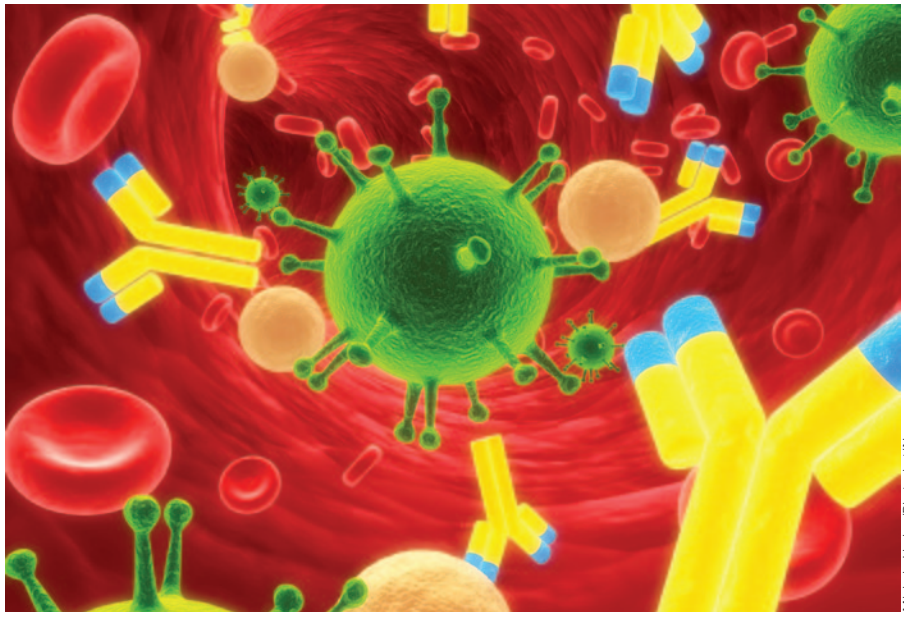
Antiretroviral drugs each block a virus-encoded enzyme—integrase, protease or reverse transcriptase—targeting different stages in the HIV life cycle. For the trial, the BMS drug was combined with Isentress (raltegravir), an integrase inhibitor, and Viread (tenofovir), a reverse transcriptase inhibitor. Of the study's 254 participants who had undergone other treatments, many had one or more regimens fail.

The BMS drug is often lumped with HIV entry inhibitors already on the market, including London-based GlaxoSmithKline's Selzentry (maraviroc) and Genentech's Fuzeon (enfuvirtide). Selzentry, a selective and reversible chemokine receptor CCR5 antagonist, binds CCR5, a co-receptor essential for most HIV isolates to infect healthy cells, whereas Fuzeon targets the co-receptor CXCR4 that other HIV isolates need to infect $CD4^+$ T cells.

But whereas antiretroviral therapies are a convenient single-pill cocktail taken once a day, Fuzeon requires twice-daily subcutaneous injections. Selzentry, a pill taken twice daily, requires a tropism test to determine whether the drug will be effective. As a result neither drug is prescribed much though Selzentry is sometimes used as a salvage therapy and occasionally as part of an initial combination therapy, says Daniel Kuritzkes, chief of the division of infectious diseases at the Brigham and Women's Hospital in Boston who serves as a consultant to BMS.

In contrast, BMS-663068 should be effective against all HIV strains except two rare subtypes. The compound is unique, says Max Lataillade, vice president of HIV development at BMS, because unlike other entry inhibitors, which prevent events after HIV docks onto CD4, the BMS drug prevents the initial interaction with CD4, and therefore immune cell entry.

But BMS-663068 is a pro-drug, processed to BMS-626529, and therefore cannot be included in a once-daily pill combination with other drugs as a first line of therapy. This, and its twice-daily dosing is why BMS-663068 is being developed for those patients who are resistant to all but two HIV drug classes. "This does not mean that after we test this compound in heavily treatment-experienced patients, that we would not follow with additional studies in lesser pretreated patients," says Lataillade.



Michele Limina/Photoshot/Newscom

Antibodies that attach to the HIV envelope could stop the virus from infecting T cells.

Antibodies against the CD4 receptor are also under investigation for their ability to block HIV entry. Both Taipei City, Taiwan–based TaiMed's ibalizumab and Hauppauge, New York–based United Biomedical's UB-421 are anti-CD4 monoclonal antibodies currently in phase 2 in patients who have been treated for HIV previously.

"The antibodies require an injection and unless it is possible to give these once a month, I don't think they will be huge players, especially when an oral agent like [BMS-663068] comes along," says Michael Saag, director of the University of Alabama Center for AIDS Research in Birmingham.

BMS-663068 ushers in the possibility of constructing new drug regimens. So far, it has not shown cross-resistance to other anti-retroviral therapies, allowing for flexible combinations. The company has initiated a pivotal phase 3 clinical trial in heavily pretreated HIV patients who have developed BMS-663068 ushers in the possibility of constructing new drug regimens. So far, it has not shown cross-resistance to other anti-retroviral therapies, allowing for flexible combinations. The company has initiated a pivotal phase 3 clinical trial in heavily pretreated HIV patients who have developed resistance to all but two classes of HIV drugs.

But mutations in gp120 that make the drug less effective have already been identified (*J. Acquir. Immune Defic. Syndr.* **64**, 505, 2013). According to Michael Farzan, an HIV researcher at the Scripps Research Institute in Jupiter, Florida, "while the data thus far are good, like for every compound and protein [against HIV], there will be escape pathways."

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Corrections

In the January 2015 issue, in the article "USDA approves next-generation GM potato" it was stated that there is no foreign DNA in the Simplot potato plant; in fact, there are trace amounts of Agrobacterium present. Additionally, the photo caption indicated that French fries made from Simplot's potatoes contain no acrylamide; there are lower levels of acrylamide in these fries than in fries made from conventional potatoes. These errors have been corrected in the HTML and PDF versions of the article.

In the March 2015 issue, in the article "Amgen's bispecific antibody puffs across finish line," the figure caption and credit referred to another news story in the issue. The error has been corrected in the HTML and PDF versions of the article.

In the March 2015 issue, in the article "First US biosimilar edges towards market," the picture caption stated that Amgen's Neupogen was the first biosimilar to be approved by the FDA, rather than saying that the first biosimilar for Neupogen had been approved by the FDA. The error has been corrected in the HTML and PDF versions of the article.