NEWS & VIEWS

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INSIDE DECEMBER'S ISSUE

THE CHALLENGE OF DEFINING HIV REMISSION

From thebody.com

Supportive Regulatory Guidance for Cure Research Requires a Clear Understanding of All Possible Outcomes, Including Remission

The term remission is increasingly being invoked in the context of cure research and, by extension, is an issue for regulatory authorities such as the U.S. Food and Drug Administration considering measurements of safety and efficacy in clinical trials. Remission, as an outcome, has been applied in a number of cases where people with HIV have interrupted antiretroviral therapy (ART) and maintained low or undetectable viral loads for some period. It is also being assessed as a possible endpoint in a clinical trial (IMPAACT P1115) aiming to test whether starting ART immediately in perinatally infected newborns might later allow for temporary or even long-term treatment interruption.

The hope is that achieving remission will represent a first step toward the discovery of a permanent cure. While this idea may seem relatively straightforward, there are important differences among reported cases in terms of how remission was achieved and significant challenges in assessing whether post-ART control of viral load leads to a state of health equivalent to that of an individual on effective ART or a comparable HIV-negative person.

Current evidence indicates that the examples of possible remission that have been reported recently (see table) fall into two categories. In the widely publicized case of the so-called Mississippi baby, in whom HIV remained undetectable for 27 months after stopping ART, and the two adults known as the Boston patients, HIV appears to have been totally inactive during the period off ART. This was likely because the reservoir of latently infected CD4+ T cells in their bodies was extremely small, lowering the probability of one of the cells becoming activated and awakening the latent HIV within it (CD4+ T cells can activate if they encounter an antigen they recognize or respond to signals from immune system proteins such as cytokines and chemokines). However, the probability was not zero, and it is thought that eventually one or more of the latently infected CD4+ T cells became activated, allowing it to generate new viruses that went on to infect new cells and cause the viral load to rebound.

Importantly, no immune responses against HIV were detectable in these three individuals until after viral load became detectable, arguing against any role of the immune system in containing the virus during the remission. In the Mississippi child, very early initiation of ART suppressed the virus before HIV-specific immunity developed, whereas in the Boston patients the maintenance of ART during their stem cell transplants (given as treatment for cancer) meant that the new immune system that developed from the donated stem cells did not encounter HIV antigens, so no virus-specific immunity was generated.

A different scenario applies in individuals referred to as post-treatment controllers, who are sometimes described as being in virological remission (the term functional cure has also been used, but is falling out of favor). The most famous examples are the VISCONTI cohort, a group of individuals in France who started ART soon after infection, remained on treatment for several years, then interrupted and maintained viral loads around or below the limit of detection (typically <20 copies/mL). At the time of the last detailed published report in March 2013, the cohort comprised 14 participants who had been off ART for an average of around 7.5 years. A brief update in a scientific review article published in January 2015 stated that this number had increased to 20, with the average time off ART at just over nine years. Another instance of virological remission that was in the news recently involves a perinatally infected French teenager in whom ART was interrupted at around age six; with the exception of two low-level detectable readings, viral load has since been maintained below the limit of detection for over 12 years.

A unifying factor that distinguishes these individuals from the Mississippi child and Boston patients is that HIV-specific immunity is present, and while the mechanisms of viral-load control are under investigation, the preponderance of opinion is that immunologic factors are most likely involved (whether adaptive HIV-specific immune responses, innate immune responses, or some combination of both).

Amid these possible examples of remission, the question whether there are implications for long-term health that may differ from those associated with ART-mediated HIV suppression has gone largely unasked. But it is critically important, both for the individuals concerned and for future regulatory assessments of interventions that might promote remission.

There is reason to be optimistic that in cases where HIV is completely inactive, there would be little or no possibility of the virus causing immunologic or health problems. Nevertheless, it would still be desirable to formally evaluate the question in clinical trials, which may be possible if IMPAACT P1115 is successful in recapitulating the remission experienced by the Mississippi child in some participants.

In post-treatment controllers, however, there is already some evidence to suggest that immune-mediated containment of viral load could come at a cost to long-term health. The evidence derives from studies of elite controllers (ECs), who naturally suppress HIV to undetectable levels without ART.

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While ECs are at a massively reduced risk of disease progression compared with untreated HIV-positive individuals with higher viral loads, it has become evident over long-term follow-up that ECs can experience a slow loss of CD4+ T cells, gradual progression to AIDS, and increases in biomarkers of cardiovascular disease. The driving factor appears to be immune activation, which, on average, is higher among ECs than in comparable HIV-negative individuals. There is also some evidence that ECs may be hospitalized more often than similar HIV-positive individuals on ART, due primarily to cardiovascular disease, but this has been reported in only one study, and it's possible that confounding factors -- such as smoking -- contributed to the difference.

The potential relevance of these observations to post-treatment controllers is highlighted by a recent update on the VISCONTI cohort at the IAS Towards an HIV Cure Symposium in July. Of the 14 individuals described in the 2013 publication, one has experienced a viral-load rebound reaching close to 100,000 copies/mL after six years off ART, necessitating reinstitution of treatment. Another has a persistently detectable viral load in the range of 100-1,000 copies/mL and a declining CD4+ T-cell count that is now below 500 cells/mm^3. A third is reported to have developed a head and neck cancer and has resumed treatment. One of the original 14 is now lost to follow-up. Of the remaining 10 still being followed, nine have viral loads less than 20 copies/mL, while one had a viral-load level of 211 copies/mL at the time of last measurement. The presentation also notes that six post-treatment controllers have been added to the cohort, explaining the reference to a total of 20 members from earlier this year. However, data are shown for only one of these individuals, who is controlling viral load but has a CD4+ T-cell count below 400/mm^3.
Several important concerns are underscored by this news:

The term virological remission tends to be truncated to just remission, which most people understand to mean a state of freedom from risk of disease. But the immune activity required to contain HIV in post-treatment controllers could be associated with negative health consequences, as has been reported in some ECs. Certainly, media descriptions of the VISCONTI cohort as examples of functional cures (which included a high-profile BBC story) were mistaken, and this term should not be used in relation to post-treatment control.

The widely reported suggestion that the VISCONTI cohort would likely not face the disease progression and health risks reported in some ECs because of lower immune activation should be viewed with skepticism. Immune activation levels in these post-treatment controllers have not been compared with those in HIV-negative individuals, and no data on inflammation levels or biomarkers of cardiovascular disease risk have been presented.

From the regulatory perspective, the benefits and risks of the HIV suppression seen in post-treatment controllers compared with that achieved by ART are currently unknown and will need to be evaluated in randomized studies. There are planned trials of ART interruption in individuals treated very early after HIV infection that may be able to look at this question if a sufficient number of participants display post-treatment control.

Since this may sound pessimistic, it should be noted that research on ECs offers reasons for hope as well as concern. There is evidence from several studies that a subset of ECs maintains extraordinarily strong suppression of HIV and shows immune activation and inflammatory gene expression profiles that closely resemble those of similar HIV-negative counterparts. And at least one reported case suggests that similarly strict control of HIV may be achievable in some post-treatment controllers. A logical implication is that the risk of HIV-related disease progression and illness would be extremely low or absent in these individuals unless levels of virus increase. These findings also imply that gradations in viral-load levels may be important even when the levels are extremely low and undetectable by standard clinical tests.

The refinement of biomarkers of immune activation and inflammation -- which have been associated with both disease progression and morbidity and mortality in population-based studies -- could also aid in the understanding of how low HIV levels may or may not affect health. Currently, there is a great deal of variability in how these biomarkers are measured in different studies, and it would be helpful to achieve consensus about how they should be evaluated in cure-related trials. Early discussions around endpoints in clinical trials where remission or post-treatment control is the goal have focused on standard virological measures (there is a proposed endpoint named virus suppression off therapy, or VSOT), which may not provide sufficient information about the prognosis of an individual who appears to be controlling viral load.

CONCLUSION

The overall message from recent research is that various forms of remission and post-treatment control are possible, but need to be better understood, particularly in terms of their long-term health implications. While the type of remission observed in the Mississippi baby and Boston patients appears ideal, it is very difficult to achieve because it requires very large reductions in the size of the latent HIV reservoir. The development of reservoir-reducing interventions is a key priority for cure research, and multiple trials of potential candidates are under way, but the task is challenging.

Post-treatment control has been posited as a more realistic goal in the near term, but there is a need to ensure that it leads to a state of health that is at least comparable to that attained on ART, if not better. When encountering terms such as remission, functional cure, and post-treatment control -- which all too frequently have been used interchangeably -- it's important to appreciate that there remains a lack of consensus as to how exactly to define them, which will hopefully be resolved as the science evolves.

PARTICIPATION & SOCIAL ACTIVITY PROGRAMS

THE PARTICPATION PROGRAM STARTS
JANUARY 01, 2016 TO DECEMBER 31. 2016
THE SOCAIL ACTIVITY PROGRAM STARTS
DECEMBER 01, 2015 TO NOVEMBER 30, 2016

HIGH COST OF HIV MEDS, OTHER DRUGS SHOULD BE TOP PRESIDENTAL CONCERN, MOST AMERICANS SAY

From TheBody.com

Rising drug costs, particularly for medications that treat chronic infections such as HIV, will likely be a hot-button issue during the 2016 presidential election cycle, according to a new poll from Kaiser Family Foundation (KFF). The survey reveals strong support across party lines for governmental action to ensure that drugs are affordable for those who need them.

The KFF telephone survey, which was conducted Oct. 14 to Oct. 20 among 1,203 American adults, found that an overwhelming majority (approximately 77% of the general public) want the president and Congress to prioritize access to "high-cost drugs" for chronic conditions. The question specified HIV, hepatitis, mental illness and cancer as examples of such conditions.

More than half of Democrats, Republicans and independents said that governmental action to lower prescription drug prices should be a top priority. Nearly half of all people surveyed would also prioritize assistance for high out-of-pocket health care costs for moderate-income people.

"Drug pricing is a very important and serious issue. The high cost of drugs is more and more of a barrier for people living with HIV to get access and adhere to their medication," Ronald Johnson, vice president of policy & advocacy at AIDS United, told TheBody.com in reaction to the findings.

"Recent research has shown keeping people in treatment helps prevent new infections. It is important for the individual, the public and for prevention," he added.

In its report on the survey, KFF notes that "[a]s some Presidential candidates begin releasing details of their health care platforms, the public's opinion of priorities in health care becomes increasingly relevant." However, medication pricing isn't a new issue. From 1998 to 2008, the amount Americans spent on prescription drugs more than doubled, according to the Centers for Disease Control and Prevention.

A report from Express Script released earlier this year found that price increases for specialty drugs, such as those used to treat HIV, largely spurred a 13% increase in prescription drug spending.

In September, the 5,000% price increase of Daraprim, a drug used to treat toxoplasmosis -- a parasitic infection that can be life threatening for people with severely weakened immune systems -- brought HIV drug pricing practices to the forefront.

At that time, both Democratic and Republican presidential candidates seized the opportunity to discuss the pricing issue.

In a tweet, presidential hopeful Hillary Clinton wrote, "Price gouging like this in the specialty drug market is outrageous." She later released a prescription drug plan that would give Medicare the ability to negotiate bulk discounts from pharmaceutical companies, cap monthly out-of-pocket costs for people with chronic ailments and hasten the arrival of cheaper generic drugs into the marketplace, among other measures.

Republican candidate and billionaire real estate mogul Donald Trump blasted the CEO of Turing Pharmaceuticals, which makes Daraprim, calling the young hedge fund manager a "spoiled brat."

Senator Bernie Sanders, D-Vt., has long been a vocal proponent of fair pricing for HIV medication. In 2011 and 2013 Sanders introduced bills intended to reward pharmaceutical companies for developing affordable, innovative HIV drugs.

"To me, one of the great moral issues of our day is that there are people in our country suffering and in some cases dying because they are not able to afford a medicine that can be produced for pennies per treatment," Sanders said in his opening statement at a 2012 Senate Subcommittee on Primary Health and Aging hearing on the high cost of HIV/AIDS drugs.

In October of this year, he paired up with fellow Democrat Rep. Elijah Cummings, a House member from Maryland, to announce the formation of a task force to investigate the rising cost of prescription drugs.

RSVP

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When your RSVP, we can ensure there is enough food for everyone.

SINGLE - TABLET HIV REGIMEN CONTAINING TENOFOVIR, ALAFENAMIDE, IMPROVES BONE AND KIDNEY SAFTEY

From TheBodyPRO.com

A new coformulation of elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild) containing tenofovir alafenamide (TAF) -- an improved prodrug of tenofovir -- offered better bone and kidney safety, while maintaining viral suppression, in patients who switched from efavirenz/tenofovir/emtricitabine (Atripla), according to a study presented at ICAAC/ICC 2015 in San Diego.

The study, which was presented by David Shamblaw, M.D., followed 376 individuals living with HIV (median age of 39) who had achieved undetectable viral loads while taking efavirenz/tenofovir/emtricitabine. Of these participants, 251 were switched to elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) and 125 remained on efavirenz/tenofovir/emtricitabine.

After 48 weeks, 96% of the TAF group and 90% of the efavirenz group maintained an undetectable viral load. In terms of bone safety, those in the TAF group had an average change of +1.44% in hip bone mineral density (BMD), compared to -0.24% in the efavirenz group ($P < .001$). Moreover, the average change in spine BMD was +0.86% for the TAF group and -0.22% for the efavirenz group ($P = .048$).

In terms of kidney safety, levels of proteinuria and specific proximal tubular proteinuria (indicators of kidney damage) were significantly lower in those in the TAF group than those in the efavirenz group.

The participants were also assessed for central nervous system (CNS) side effects, including dizziness, insomnia, impaired concentration, somnolence and abnormal dreams. At week two, those in the TAF group reported a reduction of 58% while those in the efavirenz group reported a reduction of 5%, according to Shamblaw.

Additionally, a second study examined E/C/F/TAF in patients with an estimated glomerular filtration rate (eGFR) between 30-69 mL/min. Glomerular filtration rate is a measure of how well your kidneys filter out waste products, with a number below 60 signifying kidney damage. The study followed 80 patients who had achieved undetectable viral loads, who were then switched to E/C/F/TAF. After 48 weeks, they maintained a stable eGFR and saw significant reduction in levels of proteinuria. These results suggest that E/C/F/TAF could be a safe option for patients who have impaired kidney function.

The U.S. Food and Drug Administration will decide on the new coformulation of E/C/F/TAF by early November 2015.

THE CAC IS LOOKING FOR A FEW GOOD CLIENTS

IF YOU ARE INTERESTED PLEASE CONTACT DEAN B AT deanb.odcac@outlook.com OR CALL EITHER CENTER AND ASK FOR EXT. 375 AND LEAVE YOUR INFORMATION OR CONTACT PERRY M. OR A STAFF MEMBER FOR MORE INFORMATION

GENVOYA, NEW SINGLE - TABLET HIV REGIMEN TENOFOVIR ALAFENAMIDE, APPROVED BY FDA

From TheBodyPRO.com

On Nov. 5, the U.S. Food and Drug Administration (FDA) approved elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF), which will be marketed as Genvoya, for the treatment of HIV in adults and children over 12.

E/C/F/TAF is a single-tablet combination regimen, the first FDA-approved regimen to contain tenofovir alafenamide (TAF), a prodrug of tenofovir that has been shown to be more potent at lower doses and gentler on the bones and kidneys than tenofovir disoproxil fumarate (TDF, Viread).

Previous clinical trials showed that E/C/F/TAF was noninferior to elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild), while offering better bone and kidney safety.

Another clinical trial showed that switching to E/C/F/TAF from efavirenz/tenofovir/emtricitabine (Atripla) maintained viral suppression in addition to bone and kidney safety benefits.

E/C/F/TAF is approved for treatment-naive patients, as well as adults with undetectable viral loads on other regimens, according to the FDA press release.Additionally, E/C/F/TAF is not recommended for patients with severe kidney disease, but can be taken by those with moderate kidney disease.

"Today's approval of a fixed-dose combination containing a new form of tenofovir provides another effective, once-daily complete regimen for patients with HIV-1 infection," said Edward Cox, M.D., director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research, in the press release.

The FDA will decide on two other coformulations containing TAF in early 2016: an updated version of tenofovir/emtricitabine (Truvada) at two different doses for combination with other antiretrovirals, and an updated version of rilpivirine/tenofovir/emtricitabine (Complera).

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deanb.odcac@outlook.com

DECEMBER EVENTS

01 - Positive Support Group (A) 4p - 5p
02 - Positive Support Group (E) 12p - 1p
03 - Recovery Support Group (E) 12p - 1p
04 - Support Group (A) 4p - 6p
08 - Positive Support Group (A) 4p - 5p
10 - Recovery Support Group (E) 12p - 1p
11 - Positive Support Group (E) 12p - 1p
11 - Support Group (A) 4p - 6p
12 - CAC Holiday Party (G) 3pm - 7pm
14 - Health & Wellness Group (A) 10a - 12p
14- Pain Management Group (E) 12p
14 - Latino Support Group (E) 3p - 4p
15 - Positive Support Group (A) 4p - 5p
16 - Support Group (A) 4p - 6p
16 - Positive Support Group (E) 12p - 1p
17 - Recovery Support Group (E) 12p - 1p
21 - CAC Meeting 5:30p - 7p
21 - Health & Wellness Group (A) 10a - 12p
21 - Latino Support Group (E) 3p - 4p
22 - Positive Support Group (A) 4p - 5p
23 - Positive Support Group (E) 12p - 1p
24 - Recovery Support Group (E) 12p - 1p
25 - Merry Christmas & Happy Holiday Centers Closed
28 - Health & Wellness Group (A) 10a - 12p
28 - Latino Support Group (E) 3p - 4p
28 - Pain Management Group (E) 12p

(A) Aurora Center
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(E) Elgin Center
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(G) First Congregational Church
321 Hamilton Geneva IL 60134

Happy Holidays!