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I RESEARCH WITH WOMEN AND HIV

A. Integrase inhibitors and their effectiveness and safety in women

Over the past several years leading HIV treatment guidelines in high-income countries have positioned a class of anti-HIV drugs called integrase inhibitors as the preferred option for use in combination anti-HIV therapy (ART) when initiating treatment. This is because integrase-inhibitor-containing ART is potent; in general, such combinations quickly reduce viral load. Overall, integrase inhibitors are generally well tolerated and as a class tend to have fewer drug interactions than other classes such as protease inhibitors and non-nukes.

Several integrase inhibitors are licensed in high-income countries with at least two more on the way over the next several years. Unfortunately, in the rush to licensure, some pharmaceutical companies did not recruit sufficient HIV-positive women in the initial clinical trials of integrase inhibitors, and so doctors and their female patients could not be certain about the safety of some integrase inhibitors in women. That has now been changed with the release of two important studies: Waves and Aria.

In Waves, researchers tested the integrase inhibitor elvitegravir, which is co-formulated with several other anti-HIV drugs and sold as a complete treatment under the brand names Genvoya and Stribild. Waves used the combination of drugs found in Stribild (elvitegravir + cobicistat + tenofovir DF + FTC).

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In Aria, researchers tested a competing integrase inhibitor called dolutegravir (Tivicay), which is co-formulated with two other drugs (abacavir + 3TC) to form a complete regimen in one pill that is sold as Triumeq.

The results from both Waves and Aria show that not only does integrase inhibitor–based ART work well in women but that, in general, both regimens are safe and better tolerated than the regimen based on the protease inhibitor atazanavir (Reyataz).

In this issue of *TreatmentUpdate* we have results from those clinical trials and other research with HIV-positive women.

REFERENCES:

1. Squires K, Kityo C, Hodder S, Johnson M, et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. *Lancet HIV*. 2016 Sep;3(9):e410-20.

2. Orrell C, Hagins D, Belonosova E, et al. Superior efficacy of dolutegravir/abacavir/lamivudine FDC compared with ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate/emtricitabine FDC in treatment-naïve women with HIV-1 infection: Aria study. In: Program and abstracts of the *21st International AIDS Conference*, 18-22 July 2016, Durban, South Africa. Abstract THAB0205LB.

B. Stribild in women

Waves—a randomized double-blind, placebo-controlled study—compared the impact of the following once-daily regimens in HIV-positive women who had not previously received treatment:

- Stribild – one pill that contains elvitegravir + cobicistat + tenofovir DF + FTC
- atazanavir (Reyataz) + ritonavir + tenofovir DF + FTC

After 48 weeks more women taking Stribild (87%) had an undetectable viral load (less than 50 copies/mL) compared to women taking the regimen based on atazanavir (81%). Side effects in this study were mainly related to harmless yellowing of the skin and whites of the eyes, which occurred among atazanavir users. This side effect caused more women (19) taking atazanavir to prematurely leave the study compared to the five women taking Stribild who left the study for other reasons. Stribild contains the integrase inhibitor elvitegravir. The Waves study underscores the general effectiveness and safety of elvitegravir-containing medicines in women and the leading position of integrase inhibitors in treatment guidelines.

Study details

In Waves, researchers enrolled women from the following countries:

- Belgium
- Dominican Republic
- France
- Italy
- Mexico
- Portugal
- Russia
- Thailand
- Uganda
- U.K.
- U.S.

The average profile of participants upon entering the study was as follows:

- age – 35 years
- main ethno-racial groups: black – 48%; white – 43%
- at least 75% of participants had symptom-free HIV infection
- HIV viral load – 32,000 copies/mL
- CD4+ cell count – 360 cells/mm^3
- hepatitis B virus co-infection – 4%
- hepatitis C virus co-infection – 8%
- eGFR (estimated glomerular filtration rate; an assessment of kidney health) – 106 mL/minute
- history of anxiety or depression – 20%
- use of tobacco – 25%
- use of alcohol – 50%
- use of street drugs – 3%

The average profile of women from the U.S. differed in a statistically significant manner from women outside the U.S. in the following ways:

History of anxiety or depression
- U.S. women – 53%
- non-U.S. women – 11%

Having a previous sexually transmitted infection
- U.S. women – 47%
- non-U.S. women – 30%

Recreational drug use
- U.S. women – 13%
- non-U.S. women – 1%

The study lasted for one year.

Results—Effectiveness

At the 48th week of the study the distribution of participants on each regimen whose viral load was less than 50 copies/mL was as follows:

- Stribild – 87%
- atazanavir-based – 81%

Based on this difference, Stribild was judged to be statistically superior to the atazanavir-based regimen. However, bear in mind that part of the reason for Stribild's apparent superiority (having more people on this regimen at week 48 with a suppressed viral load) is that a large fraction of women taking atazanavir dropped out of the study because of side effects.

Adverse events

The term *adverse events* refers to a range of unfortunate events that can happen during a clinical trial. Some of these events can be caused by the study medications, in other cases by an underlying illness or disease process or even by events (such as accidents) that may have nothing to do with the trial.

According to the researchers, most adverse events in the study were reported as "mild or moderate in severity." More severe adverse events were distributed as follows:

- Stribild – 8%
- atazanavir-based regimen – 10%

No one died while in the study.

Discontinuations due to adverse events

The proportions of women who prematurely left the study due to adverse events were as follows:

- Stribild – 2%
- atazanavir-based – 7%

Reasons for prematurely leaving the study were as follows:

Stribild
- rash and nausea
- rash and yellowing of the skin
- elevated levels of liver enzymes in the blood
- indigestion
- stomach ulcer
- tuberculosis

Atazanavir-based regimen
- yellowing of the skin
- rash (in some cases this was severe or life-threatening)
- severe kidney injury
- decreasing eGFR

Focus on side effects

Side effects were distributed as follows:

Headache
- Stribild – 5%
- atazanavir-based regimen – 2%

Nausea
- Stribild – 11%
- atazanavir-based regimen – 10%

Vomiting
- Stribild – 5%
- atazanavir-based regimen – 3%

Diarrhea
- Stribild – 3%
- atazanavir-based regimen – 4%

Dizziness
- Stribild – 3%
- atazanavir-based regimen – 2%

Rash
- Stribild – 2%
- atazanavir-based regimen – 5%

Fatigue
- Stribild – 1%
- atazanavir-based regimen – 3%

Decreased appetite
- Stribild – 3%
- atazanavir-based regimen – 1%

Jaundice (yellowing of the skin)
- Stribild – 0%
- atazanavir-based regimen – 10%

Yellowing of the whites of the eyes (ocular icterus)
- Stribild – less than 1%
- atazanavir-based regimen – 12%

Focus on lab tests

Abnormal blood test results included the following:

Elevated levels of the liver enzyme ALT
- Stribild –1%
- atazanavir-based regimen – 2%

Elevated levels of the liver enzyme AST
- Stribild – 2%
- atazanavir-based regimen – 2%

Detectable sugar in the urine
- Stribild – 0%
- atazanavir-based regimen – 2%

In general, most abnormal blood test results were graded as mild or moderate in severity among women who used Stribild. In contrast, among women who used an atazanavir-based regimen, most abnormal blood test results were graded severe or very severe. This difference arose chiefly because of elevated levels of the waste product bilirubin. This effect is called hyperbilirubinemia and is a well-known side effect associated with atazanavir. In such cases, this elevated level of bilirubin in the blood is generally considered harmless and returns to normal when the person stops taking atazanavir.

There were no clinically significant differences in blood test results concerning cholesterol and triglycerides between people on the different study regimens.

Changes in eGFR associated with the study drugs were modest and similar between study regimens. This was also the case for differences in bone density.

Muscle and fat

One change that was significantly different between the two regimens was related to changes in the amount of muscle tissue. Women who used Stribild gained an average of 866 grams (almost two pounds) of muscle. In contrast, women who used an atazanavir-based regimen did not significantly gain any muscle but rather they gained 1.4 kg (about three pounds) of fat. Women who used Stribild did not gain significant amounts of fat.

Pregnancy

During the study 24 women became pregnant and 16 of them—eight taking Stribild and eight taking an atazanavir-based regimen—chose to continue taking the study drugs.

Miscarriages occurred in the first three months of the study among four women—two on each study regimen. As for the 12 remaining pregnant women in the study, their pregnancies and birthing process were uncomplicated and none of the babies had birth defects.

Key points

Both study regimens were generally safe and effective. However, Stribild was statistically superior to the regimen based on atazanavir. This statistical superiority was driven by the greater rate of discontinuations among women taking atazanavir who developed side effects. These side effects were mostly rash and elevated levels of bilirubin in the blood.

Rates of premature departure from the study were greater than previously reported in other trials of atazanavir-based regimens.

REFERENCE:

Squires K, Kityo C, Hodder S, Johnson M, et al. Integrase inhibitor versus protease inhibitor–based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. *Lancet HIV*. 2016 Sep;3(9):e410-20.

C. Dolutegravir in women

In a study called Aria, researchers tested the following two regimens with nearly 500 HIV-positive women:

- Triumeq – one pill that contains dolutegravir + abacavir + 3TC
- atazanavir (Reyataz) + ritonavir + tenofovir DF + FTC

Women who entered the study had not previously used anti-HIV drugs.

After 48 weeks, 82% of Triumeq users and 71% of women taking an atazanavir-based regimen had a viral load less than 50 copies/mL. This difference gave Triumeq statistical superiority over the atazanavir-containing regimen. This was driven in part by more participants who took atazanavir dropping out for reasons due to side effects.

Study details

Researchers from many countries, including Canada, Spain, South Africa, Russia, Thailand, the U.S. and elsewhere, screened 705 volunteers but found only 495 who were suitable for the study. They then randomly assigned these 495 women to receive one of the study regimens as follows:

- Triumeq
- an atazanavir-based regimen

Participants knew which treatment they received, as there were no placebos used.

The average profile of participants upon entering the study was as follows:

- age – 37 years
- main ethno-racial groups: white – 44%; black – 42%; Asian – 9%
- 85% of participants had no symptoms of HIV disease
- HIV viral load – 32,000 copies/mL
- CD4+ count – 375 cells/mm^3
- 7% had been exposed to hepatitis C virus

The main part of the study lasted for 48 weeks. After this time, participants who were already taking Triumeq continued to receive the drug from the study sponsor, ViiV Healthcare (which also makes Triumeq), until Triumeq was approved in their country. We will report on the results up to the 48th week of the study.

Results—Effectiveness

As mentioned earlier, at week 48 of the study 82% of the women taking Triumeq and 71% of those taking an atazanavir-based regimen had a viral load less than 50 copies/mL.

Here is what happened to the remaining participants:

Virological non-response (these participants either did not get their viral load below the 50 copy mark and/or they did but were unable to keep it there):

- Triumeq – 6%
- atazanavir-based regimen – 14%

There was no virological data (usually because participants left the study prematurely) for the following participants:

- Triumeq – 12%
- atazanavir-based regimen – 15%

High viral loads at baseline

Among participants who entered the study with a high viral load (more than 100,000 copies/mL), here are the proportions with a suppressed viral load (less than 50 copies/mL) at week 48:

- Triumeq – 80%
- atazanavir-based regimen – 64%

Among participants who entered the study with a low CD4+ count (350 or fewer cells), here are the proportions with a suppressed viral load at week 48:

- Triumeq – 85%
- atazanavir-based regimen – 72%

Adverse events

The term *adverse events* covers a broad range of unfortunate health-related incidents that can occur during a clinical trial. Some of these incidents may be related to drug side effects. However, some adverse events could be related to the underlying infection, disease process or even, in some cases, events outside the clinical trial, such as an accident.

Overall adverse events of moderate, severe or very severe intensity were distributed as follows:

Nausea
- Triumeq – 13%
- atazanavir-based regimen – 14%

Diarrhea
- Triumeq – 5%
- atazanavir-based regimen – 7%

Indigestion
- Triumeq – 2%
- atazanavir-based regimen – 6%

Headache
- Triumeq – 2%
- atazanavir-based regimen – 6%

Yellowing of the whites of the eyes (ocular icterus)
- Triumeq – 0%
- atazanavir-based regimen – 7%

Yellowing of the skin (Jaundice)
- Triumeq – 0%
- atazanavir-based regimen – 5%

The proportion of participants who left the study because of side effects was distributed as follows:

- Triumeq – 4%
- atazanavir-based regimen – 7%

One woman who was taking Triumeq died and investigation revealed that her death was not related to the study medicines.

Focus on mental health

Dolutegravir belongs to a class of anti-HIV drugs called integrase inhibitors. *All* integrase inhibitors have been associated with reports of mental health issues (usually sleeping problems, anxiety and/or depression) in a small proportion of patients who use them. Researchers are not sure why some people develop this side effect.

In previous clinical trials, rates of neuro-psychiatric side effects among dolutegravir users were relatively low, usually between 2% and 4%. Since the licensure of dolutegravir several years ago (in Trivicay and Triumeq) there have been reports of mental health issues in a minority of participants who used this drug. Unfortunately, many of these reports arise from studies that were not robustly designed, so drawing firm conclusions from them about the use of dolutegravir and possible mental health issues is fraught with difficulty. Also, depression and anxiety are relatively common issues among HIV-positive people regardless of the type of treatment they take.

In Aria, the overall distribution of neuro-psychiatric side effects was as follows:

- Triumeq – 14%
- atazanavir-based regimen – 14%

The distribution of specific neuro-psychiatric side effects was as follows:

Difficulty falling asleep or staying asleep
- Triumeq – 4%
- atazanavir-based regimen – 4%

Anxiety
- Triumeq – 2%
- atazanavir-based regimen – 3%

Depressive illness (includes depression and related problems)
- Triumeq – 3%
- atazanavir-based regimen – 4%

Thoughts of suicide
- Triumeq – 2%
- atazanavir-based regimen – 1%

Panic attacks
- Triumeq – less than 1%
- atazanavir-based regimen – less than 1%

Agitation
- Triumeq – less than 1%
- atazanavir-based regimen – 0%

Bipolar illness
- Triumeq – less than 1%
- atazanavir-based regimen – 0%

There were no reports of the following neuro-psychiatric issues:

- confusion
- hallucinations
- psychosis
- suicide

Based on the results of Aria, about 14% of women who used Triumeq or an atazanavir-based regimen developed mental health issues, mostly related to problems with sleep, anxiety or depression.

REFERENCE:

Orrell C, Hagins D, Belonosova E, et al. Superior efficacy of dolutegravir/abacavir/lamivudine FDC compared with ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate/emtricitabine FDC in treatment-naïve women with HIV-1 infection: Aria study. In: Program and abstracts of the *21st International AIDS Conference*, 18-22 July 2016, Durban, South Africa. Abstract THAB0205LB.

D. Viral load and some hormonal and metabolic issues in women

HIV infection has always been associated with reports of complex hormonal and metabolic abnormalities. Historically, the majority of such reports have been in HIV-positive men. A team of researchers in Vancouver, British Columbia, has been conducting several studies with women. In their latest analysis, the Vancouver researchers have focused on measuring a range of hormones and fatty substances in blood samples from HIV-positive women. They found that factors such as increasing age, BMI (body mass index) and, in some cases, having a high viral load prior to starting ART were associated with hormonal and metabolic abnormalities.

Study details

Researchers recruited 192 participants between 2008 and 2012 for their study. Upon entering the study, the average profile of participants was as follows:

- age – 40 years
- main ethno-racial groups: white – 44%; indigenous – 30%; black – 16%
- most women were overweight
- hepatitis C virus co-infection – 27% currently had HCV
- use of tobacco – 52% were smokers
- substance use – 34% used substances
- lowest-ever CD4+ count – 190 cells/mm^3
- current CD4+ count – 470 cells/mm^3
- proportion with an HIV viral load of 100,000 copies/mL or higher – 47%
- proportion with an HIV viral load of less than 50 copies/mL – 40%
- duration of HIV infection – 11 years

Results—Hormonal and metabolic abnormalities

The researchers found that, overall, 58% of participants had at least one abnormal hormonal or metabolic test result.

Common hormonal/metabolic issues were as follows:

- cholesterol or triglycerides – 43%
- thyroid hormone(s) – 15%
- blood sugar – 13%

Key factors associated with these abnormalities were increasing age (the older a woman, the greater the risk of having one or more of these abnormalities) and having had a high viral load (100,000 copies/mL or greater).

Focus on specific abnormalities and other associations with them

Thyroid hormones

Women who had a high viral load in the past and who were taking what the researchers termed "psychoactive medications" (drugs to help treat anxiety, depression, psychosis, sleeping problems and so on) were associated with an increased risk for having abnormal thyroid hormone levels. This should not be misinterpreted to mean that such drugs cause thyroid hormone problems. Rather, it is possible, likely even, that at least some of these women with abnormal thyroid hormone levels had mental health issues and were being treated for them. Indeed, symptoms of abnormal thyroid hormone levels (regardless of HIV infection) can include sleeping problems, anxiety and/or depression. Furthermore, these drugs do not generally cause thyroid hormone abnormalities in HIV-positive people.

Blood sugar

Participants who were older and overweight were more likely to develop problems controlling their blood sugar levels (this is seen in pre-diabetes and diabetes). A similar problem can be seen in HIV-negative women who are older and overweight.

Abnormal cholesterol and triglycerides

In general, as all people age, problems maintaining normal levels of cholesterol and triglycerides occur.

The present study confirmed that these problems occur among HIV-positive women as they age.

Bear in mind

The present study was based on tests and assessments done at one point in time. Such analyses are cross-sectional and are good at finding associations but cannot prove cause and effect. That is, they cannot prove that some thing or event results in certain consequences. However, cross-sectional studies can be a useful step when initially exploring an idea. If the cross-sectional study finds something of interest to researchers, they can then engage in the laborious and time-consuming process of writing a grant proposal for a more robustly designed study and submitting the grant proposal to a funding agency in the hope that it gets highly rated when it is reviewed so it can be funded. According to sources in the scientific community, a large majority of grants (about 85%) submitted to major funding agencies, such as the Canadian Institutes of Health Research (CIHR) in Canada or the National Institutes of Health (NIH) in the U.S., do not get funded, even if such grants are about compelling biomedical issues.

The capacity of the researchers in the present study to extract more value from their analysis was also hobbled by their inability to determine whether the hormonal and metabolic problems that they found were present before or after HIV infection occurred.

A key finding from this study is the association between having a high viral load in the past and an increased risk for having a hormonal or metabolic abnormality. This intriguing connection needs to be explored in another study to confirm that it exists.

At the time the study was done, only about 40% of participants had a suppressed viral load. The Vancouver researchers should consider performing an updated analysis of viral loads, and if there are women whose viral loads are not less than 50 copies/mL, they should undertake research to explore the reasons for this. Such a study could be useful for clinics, community groups and health authorities to develop ways to help women in Vancouver achieve the better health that comes from an undetectable viral load.

Another finding was that 52% of the women were smokers. This figure is high. As smoking is associated with many harms and reduced survival, another possible future study in Vancouver could explore ways to help these women quit.

REFERENCE:

Sokalski KM, Chu J, Mai AY, et al. Endocrine abnormalities in HIV-infected women are associated with peak viral load – the Children and Women: AntiRetrovirals and Markers of Aging (CARMA) Cohort. *Clinical Endocrinology* (Oxf). 2016 Mar;84(3):452-62.

E. Factors linked to falling in middle-aged women

Thanks to the widespread availability of potent combination anti-HIV therapy (ART) in Canada and other high-income countries, HIV-positive people are living longer and many will likely enter their senior years. However, as HIV-positive people age, they become at increased risk for aging-related complications, just like everyone else. One such complication is falling. Such an unexpected event whereby people lose their balance, slip or trip and land on the floor or ground (sometimes hitting a piece of furniture on the way down) can have serious consequences for some people.

Researchers across the U.S. interviewed 650 middle-aged women at high risk for HIV and 1,412 HIV-positive women about falling in the past six months of their lives. They also collected blood samples for assessment. They found that the rate of falls was similar—about 19% regardless of HIV status. In analysing many factors, researchers therefore confirmed that HIV infection was not a factor linked to an increased risk of falling. Instead, the following factors were associated with an increased risk of falls:

- older age
- currently using marijuana
- problems with memory and thinking clearly (neurocognitive problems)
- injured nerves in the feet, legs and/or hands (peripheral neuropathy)

Study details

The Women's Interagency HIV Study (WIHS, pronounced wise) is an ongoing study that has been monitoring the health of women with or at high risk for HIV infection. The reason that HIV-

negative women are included in WIHS is that these women come from the same communities as HIV-positive participants and serve as a useful comparison when performing lab tests and other assessments. Women recruited to WIHS come from clinics in the following cities:

- Atlanta, Georgia
- Birmingham, Alabama
- Brooklyn, New York
- Bronx, New York
- Chapel Hill, North Carolina
- Chicago, Illinois
- Miami, Florida
- San Francisco, California
- Washington, DC

Over the years, researchers with WIHS have produced many useful reports on the health of women with HIV. A major strength of WIHS is that it recruits women of similar socio-economic backgrounds. In this report we focus on the findings among HIV-positive women.

The average profile of participants upon entering WIHS was as follows:

- age – 48 years; the majority of women (74%) were between the ages of 40 to 59
- 37% had a history of AIDS
- lowest-ever CD4+ count – 274 cells/mm^3
- current CD4+ count – almost 600 cells/mm^3
- 65% had an undetectable viral load
- 49% had higher-than-normal blood pressure
- 19% had type 2 diabetes
- 12% had hepatitis C virus co-infection
- 11% had kidney dysfunction

Other health issues:

- 47% were obese
- 21% had injured nerves in their feet, legs and/or hands
- 12% had problems with memory and thinking clearly

Regarding substance use and mental health:

- 38% currently smoked tobacco
- 17% currently used marijuana
- nearly 90% had less than three drinks of alcohol-containing beverages per week
- 32% had symptoms of depression

Use of medicines that affect the brain (referred to as "CNS drugs" by the researchers) was as follows:

- 27% used antidepressants
- 13% used antiseizure drugs
- 12% used sedatives
- 10% used antipsychotics
- 4% used muscle relaxants

Results—Fear of falling

When researchers asked HIV-positive women about their fear of falling, they grouped the women's responses as follows:

- not at all afraid – 62%
- a little – 21%
- quite a bit – 7%
- very much – 10%

Here is the distribution of falls women reported in the past six months:

No falls
- HIV positive – 81%
- HIV negative – 82%

One fall
- HIV positive – 9%
- HIV negative – 8%

Two or more falls
- HIV positive – 9%
- HIV negative – 10%

(Note: Due to rounding, numbers may not total 100%.)

These differences in rates of falls between HIV-positive and HIV-negative women were not statistically significant.

Risk factors for multiple falls

Taking many possible factors into account, researchers found that the presence of the following health issues was linked to an increased risk of falling:

- age 50 to 59 years
- current and past marijuana use
- neurocognitive problems
- injured nerves in the feet, legs and/or hands

- using CNS drugs that affect the brain (the more of these drugs used, the greater the risk of falling)
- type 2 diabetes

The following factors were *not* linked to an increased risk of falling:

- HIV infection
- CD4+ cell count
- viral load
- specific HIV medicines (for instance, efavirenz, sold as Sustiva, Stocrin and in Atripla, is known to cause dizziness and many other side effects that can affect the brain)

Compare and contrast

The researchers underscored that about one-third of older HIV-negative people in the U.S. fall each year. Furthermore, they stated that about "10% of these falls [result] in injury that requires medical attention." In comparison, the researchers noted that "among our 198 participants 60 year or older, about 25% reported [falls] in the prior six months."

Bear in mind

1. Falls and their consequences—in some cases broken bones—are part of a cluster of issues that researchers call "geriatric syndromes." These are conditions/problems that are relatively common among elderly people. The WIHS team noted that geriatric syndromes are "associated with poor outcomes, including disability, frailty, reduced quality of life, loss of independence and [and increased risk of death]."

   As HIV-positive people tend to have reduced bone density, falling may increase their risk of fractures.

2. The WIHS analysis found a connection between the use of drugs that affect the brain and an increased risk of falling. Other studies with HIV-negative elderly people have found that the use of such drugs is also associated with an increased risk of falling.

3. The study was based on participants' self-reports about falls in the past six months. It is possible that some participants may have underestimated their falls, since some of them had memory problems.

4. It would have been useful if the present study had collected data on other common factors related to falls, such as a history of the following:

   - visual difficulties
   - stroke
   - heart attack
   - the sudden onset of low blood pressure that can occur when a person sits up, stands or suddenly gets out of bed (orthostatic hypotension), resulting in dizziness, blurred vision, light-headedness and loss of consciousness

5. The researchers only analysed information collected about falls that participants could recall occurring in the past six months. WIHS started asking participants about falls in 2014. As time goes by, it would be useful for WIHS to continue to ask about falls and document and monitor any changes that occur over the long term. Such documentation would be useful, as many HIV-positive people are aging.

6. The researchers stated that they identified "a number of modifiable risk factors for falls, including use of multiple CNS active medications and substance use, which could be important areas to target in fall prevention as women age."

REFERENCE:

Sharma A, Hoover DR, Shi Q, et al. Falls among middle-aged women in the Women's Interagency HIV Study. *Antiviral Therapy*. 2016; *in press*.

F. Response to HPV vaccine best in women with undetectable HIV viral load

Human papillomavirus (HPV) is a common sexually transmitted germ. Many different strains of HPV exist and can cause different complications such as ano-genital warts and anal, cervical and vulvar cancer, as well as cancers of the throat and tongue.

There are three licensed HPV vaccines as follows:

- Cervarix – provides protection against HPV 16 and 18 (these can cause anal and cervical cancer)
- Gardasil – provides protection against HPV 6 and 11 (these can cause ano-genital warts) as well as HPV 16 and 18
- Gardasil 9 (the newest vaccine) – provides protection against a broad range of HPV including 6, 11, 16, 18, 31, 33, 45, 52 and 58

In tests with HIV-negative men and women all of these vaccines are effective. However, there are less data on their safety and effectiveness in HIV-positive women.

A team of researchers across Canada in collaboration with the CIHR HIV Clinical Trials Network has reported results from a clinical trial of Gardasil in 310 HIV-positive women. The researchers found that the vaccine was safe. Furthermore, women whose HIV viral load was undetectable when they received the first of three injections of Gardasil produced significantly more antibodies to HPV than women whose HIV viral load was not undetectable.

The study researchers encourage doctors and nurses to consider timing the use of Gardasil once their patients' HIV viral loads have become undetectable to "optimize" the response to this vaccine.

Study details

Researchers enrolled participants between 2008 and 2012.

The average profile of the 310 women upon entering the study was as follows:

- age – 38 years
- major ethno-racial groups: black – 44%; white – 36%; Indigenous – 13%
- duration of HIV diagnosis – eight years
- CD4+ cell count – 510 cells/mm^3
- proportion with a viral load less than 50 copies/mL – 72%

At the start of the study, participants received an injection of one dose of Gardasil into muscle. Subsequent doses were given two and six months later.

Note that Gardasil is not a live vaccine, it is made from proteins taken from HPV; it cannot cause HPV infection.

What happened to participants?

As with all clinical trials, some participants move, lose interest or stop making visits to their study clinic. In total, 310 participants received at least one dose of Gardasil. A smaller group, 277 (89%) participants, received all three doses of the vaccine. Of these, 272 were negative for HPV antibodies and its genetic material at the start of the study for at least one of the HPV strains that were targeted by the vaccine. This indicates that they were not likely infected with those strains of HPV.

Results

After the seventh month of the study, the proportion of women with antibodies against HPV proteins found in Gardasil was more than 90% and in some cases as high as 98% (depending on the protein that represented HPV strains). The proportions of women with antibodies against specific HPV strains were distributed as follows:

- HPV 6 – 93% of women had antibodies
- HPV 11 – 94% of women had antibodies
- HPV 16 – 98% of women had antibodies
- HPV 18 – 67% of women had antibodies

Vaccine success

Researchers found that, in general, HIV-positive women had significantly greater levels of antibodies to HPV compared to data collected in previous trials with HIV-negative women. The exception was levels of antibodies to HPV 18, which was lower in HIV-positive women than in HIV-negative women in previous trials.

Also, the study team found that HIV-positive women whose HIV viral load was suppressed at the time they were vaccinated subsequently had the best response to Gardasil. This link between a suppressed HIV viral load and response to Gardasil was independent of participants' CD4+ cell counts.

Safety

Nurses observed participants for 30 minutes after each vaccination for any side effects that might have

immediately occurred. Furthermore, participants were telephoned 48 hours after each vaccination to discuss any potential side effects that might have occurred.

A total of 36% of participants reported one or more vaccine-related side effects, most commonly distributed as follows:

- pain at the injection site – 30%
- redness at the injection site – 6%
- swelling at the injection site – 6%

Side effects affecting other parts of the body were as follows:

- 20% of participants had headache, fever and fatigue that were clearly linked to having received the vaccine

Note that *all* side effects were temporary and resolved without any serious consequences.

Two women died during the study: One death was caused by a drug overdose 129 days after her third vaccination; the other death occurred 22 days after her third vaccination and was caused by the AIDS-related illness PML (progressive multifocal leukoencephalopathy). Investigation found that the HPV vaccine was not associated with these deaths.

A total of 41 women had 44 pregnancies during the four-year study. The results of these pregnancies were as follows:

- 23 were live births
- 16 were terminated
- 4 were miscarriages
- in one case researchers did not know the outcome

The vaccine was not linked to any adverse effect on the course of pregnancy or birth defects.

Key points

The present Canadian study found that Gardasil is safe and effective at producing relatively high levels of antibodies against HPV strains 6, 11, 16 and 18 in HIV-positive women.

Women who had an undetectable HIV viral load when they received their first vaccination of Gardasil subsequently had significantly greater levels of antibodies to HPV compared to women who did not have an undetectable HIV viral load. This finding caused the study team to encourage doctors and nurses to help their HIV-positive patients achieve an undetectable viral load status before initiating HPV vaccination.

Resource:

HPV, cervical dysplasia and cervical cancer – CATIE fact sheet

REFERENCE:

Money DM, Moses E, Blitz S, et al. HIV viral suppression results in higher antibody responses in HIV-positive women vaccinated with the quadrivalent human papillomavirus vaccine. *Vaccine*. 2016 Sep 14;34(40):4799-806.

G. Background on bacterial vaginosis in women

It is normal to have a variety of bacteria and a small amount of fungi in the vagina. However, some women can develop an imbalance in the bacteria in their vagina and a condition called bacterial vaginosis (BV) can develop. BV may or may not cause symptoms in every case. According to the Mayo Clinic, the following symptoms are associated with BV:

- a thin white or green fluid that comes from the vagina
- a fishy odour from the vagina
- vaginal itching
- a burning sensation while urinating

Women with these symptoms should see their doctor for an assessment. A sample of fluid from the vagina can be collected and sent to a lab for testing.

Known risk factors for BV include the following:

- having multiple sex partners or a new sex partner
- douching can upset the normal balance of bacteria in the vagina, but not all researchers agree about the precise role of douching on the risk of BV

BV can have serious implications for women's health, including the following:

- an increased risk for becoming infected with sexually transmitted infections, including HIV, herpes, chlamydia and gonorrhea
- an increased risk for developing pelvic inflammatory disease (PID)
- an increased risk among pregnant women for giving birth prematurely

Common treatments for BV include the following:

- metronidazole (Flagyl) tablets taken orally
- metronidazole gel that is placed in the vagina
- clindamycin cream that is placed in the vagina

For further information about the diagnosis and treatment of BV, see Management and Treatment of Specific Syndromes in the Canadian STI guidelines:

http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/section-4-8-eng.php

H. Bacterial vaginosis—some research issues

As mentioned earlier in this issue of *TreatmentUpdate*, bacterial vaginosis (BV) is the result of an imbalance in the bacteria that live in the vagina.

Emerging research ideas

Compared to many other conditions, research on BV seems to move at a slower pace. Despite this, there are some emerging themes in BV research. Readers should note that these ideas are preliminary and under study; as a result, the issues captured by these ideas may not yet be widely embraced by all researchers and doctors who study and care for women with BV.

The likely spread of BV

The cause and triggers of the imbalance in vaginal bacteria that is the hallmark of BV are unclear. Some research suggests that BV is sexually transmitted: The most significant risk factor for BV is sex with a new partner. Recurrent outbreaks of BV have been linked to sex with the same partner. Furthermore, women who have sex with men and who have recovered from BV are less likely to redevelop this problem if their male partner uses a condom.

Is it one germ or several?

Some researchers think that one type of bacteria—*G. vaginalis*—plays a key role in BV. Other researchers think that a group of bacteria work to enable a better environment within the vagina for themselves, and, as a result, cause BV.

Sexual networks

Some studies have found an increased risk of BV in women of African descent and white women who have sex with men of African descent. Researchers are not certain as to the reasons for this but suspect that the bacteria that cause BV are present in some sexual networks.

Treatment issues

Recommended treatments for women with symptoms of BV include the following:

- tablets of metronidazole (Flagyl) taken every day for one week
- metronidazole gel applied intravaginally for five consecutive days
- clindamycin cream applied intravaginally for seven days

These treatments generally work in 75% to 85% of cases. However, BV often recurs or relapses sometime after a course of treatment.

Researchers are not certain why relapse with BV is common but speculate that the bacteria that cause BV likely produce a thin sticky layer (the technical name for this is biofilm) that helps them adhere to the walls of the vagina. This biofilm may also provide some protection from antibiotics.

Scientists are studying the ability of several compounds to disrupt the biofilm associated with BV.

Friendly bacteria

Researchers are studying strains of harmless and friendly bacteria that live in the body. They are testing different combinations of such friendly bacteria (called probiotics) taken orally in capsules.

Most clinical trials of probiotics in women with BV have not resulted in high rates of cure or prevention. However, these disappointing results may have occurred because scientists tested what one research team has called "poorly chosen probiotic candidates." Emerging research suggests that new formulations of probiotics, including ones containing the bacteria *L. crispatus*, may be worth exploring in well-designed clinical trials.

Partner treatment

As emerging research suggests that BV appears to be sexually transmitted, perhaps clinical trials where the woman's partner is also treated may be a useful step forward. In the case of women with male partners, researchers are not certain which part of the male genital tract is the main source (or reservoir) of such bacteria. If such bacteria are only resident on the skin of the penis, then creams or gels could be used to treat the male partner. However, if the reservoir for BV-causing bacteria is inside the penis or other internal parts of the male genital tract, then the use of antibiotics taken orally may be a more fruitful application to explore.

Outside as well as inside

Many practices have been thought to be a trigger of BV. However, researchers have found that exposure to the following products is not clearly linked to the development of BV:

- sanitary pads
- panty liners
- sprays
- powders
- towelettes

In some studies vaginal douching has been linked to an increased risk for developing BV. Bear in mind that in most of these studies researchers have found that "women reported douching for symptoms or hygiene." As a result, it is not clear if these women already had BV prior to douching. Also, researchers have stated that "douching is strongly linked to sexual behaviour" and this makes it difficult to know if BV results from douching or the sexual exposure that occurs after douching. Taking the totality of BV research into account, some scientists think that douching may be a co-factor for the development of BV in women, particularly those with an already somewhat abnormal bacterial balance in their vaginas.

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I. Bacterial vaginosis in HIV-positive and HIV-negative women

Research teams in the U.S. have been studying the health issues of women with or at high risk for HIV infection as part of a project called the Women's Interagency HIV Study (WIHS, pronounced wise). Analyses of WIHS have produced many useful reports over the years. A recent WIHS analysis has focused on the diagnosis of BV in 3,730 women (964 without HIV and 2,766 with HIV). These women were monitored for about 11 years. Over the course of the study, 55% of HIV-negative and 47% of HIV-positive women were diagnosed with BV; this difference was statistically significant. The researchers also found that 43% of women who were treated for BV had a recurrence within a year. This was not affected by HIV status.

The WIHS researchers noted that women in their study were "dissatisfied with current therapies" and they encouraged doctors caring for women with BV to consider the following possibilities:

- home screening of BV (sending samples of vaginal fluid to a lab)
- use of probiotics to help reduce the recurrence of BV

- provision of antibiotics in advance of a recurrence of BV so that patients can "use when symptoms recur to minimize delay arising from the need for a [visit to the doctor]."

REFERENCE:

Massad LS, Evans CT, Kang R, et al. Correlates of bacterial vaginosis over long-term follow-up: Impact of human immunodeficiency virus infection. *AIDS Research and Human Retroviruses*. 2016; *in press*.

Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

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The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

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