I ANTI-HIV AGENTS

A. Dual therapy with raltegravir and darunavir

The leading U.S. HIV treatment guidelines developed by the U.S. Department of Health and Human Services (DHHS) for adults have several regimens that it recommends from which doctors and their patients can choose for the initial therapy of HIV. These regimens consist of a combination of three active drugs.

In the previous issue of TreatmentUpdate, we presented information about simplified regimens. In this issue, we have a report on one of the largest clinical trials of simplified therapy testing two powerful and generally well-tolerated anti-HIV drugs: darunavir (Prezista) + raltegravir (Isentress). This combination was given to people who had not previously used anti-HIV therapy, and researchers found that after two years dual therapy was roughly as effective as standard triple therapy containing darunavir.

In the years ahead, it will be interesting to see what treatment guideline committees, such as those convened under the aegis of the DHHS, have to say about starting therapy with simplified regimens.
Study details

Researchers in Europe conducted a clinical trial comparing standard therapy with a simplified regimen of two active drugs for the initial therapy of HIV. The two regimens are as follows:

- darunavir 800 mg/day + ritonavir (Norvir) 100 mg/day (both drugs once daily) + raltegravir (Isentress) 400 mg twice daily
- darunavir 800 mg/day + ritonavir 100 mg/day + Truvada (a fixed-dose regimen of two drugs: tenofovir + FTC)

Note that because ritonavir is given at a low dose, its sole purpose is to raise, or boost, levels of the protease inhibitor darunavir. At low doses, ritonavir does not have any significant anti-HIV activity so it is not counted as part of an active regimen. When used with ritonavir, darunavir has very powerful anti-HIV activity.

The other main drug used in this study was raltegravir, the first integrase inhibitor to become available. Raltegravir has powerful anti-HIV activity when used together with boosted darunavir.

Although researchers randomly assigned participants to the study regimens, participants knew which drugs they received; no placebos were used.

In this clinical trial, called NEAT 001/ANRS 143, researchers collected data for at least 96 weeks from participants in 15 countries. The average profile of participants at the start of the study was as follows:

- 88% men, 12% women
- HIV viral load – 58,000 copies/ml
- about 1/3 of participants had a viral load greater than 100,000 copies/ml
- 6% had a viral load greater than 500,000 copies/ml
- CD4+ count – 330 cells
- 5% had AIDS
- 4% had hepatitis C virus co-infection

Of the 805 participants enrolled, 401 were assigned to receive dual therapy and 404 others to receive standard triple therapy.

Results—Changes in viral load

The proportions of participants whose viral load was less than 50 copies/ml at different points in the study were distributed as follows:

48 weeks
- dual therapy – 89% had a viral load less than 50 copies/ml
- triple therapy – 91% had a viral load less than 50 copies/ml

96 weeks
- dual therapy – 89% had a viral load less than 50 copies/ml
- triple therapy – 93% had a viral load less than 50 copies/ml

Focus on virologic failure

According to the study design, participants who had a viral load in their blood of at least 50 copies/ml at week 32 were considered to have virologic failure. These cases were distributed as follows:

- dual therapy – 27 cases of virologic failure at the 32nd week of the study
- triple therapy – 28 cases of virologic failure at the 32nd week of the study

After week 32, additional participants who developed virologic failure were distributed as follows:

- dual therapy – 32 cases of virologic failure
- triple therapy – 22 cases of virologic failure

Genotypic resistance testing was done on a subgroup of all participants with virologic failure as follows:

- dual therapy – 28 participants
- triple therapy – 13 participants

There was no evidence of HIV developing resistance to protease inhibitors—the category to which darunavir belongs—in blood samples from participants on either study regimen.

In five cases researchers found evidence that HIV had developed major mutations against raltegravir.

Effectiveness and statistics

Prior to launching the study, the researchers developed a complex series of goals by which to assess the effectiveness of each regimen. These
were a combination of virologic and clinical results (called endpoints), some of which we report. When the study results were analysed this way, the differences between regimens were relatively small. According to the statistical design that underpinned the study, researchers then declared that, overall, the experimental regimen of raltegravir + darunavir + ritonavir was “non-inferior” to standard triple therapy with darunavir + ritonavir + tenofovir + FTC. This interpretation does not mean that the regimens are equivalent, merely that, overall, the dual therapy in this study was not worse than triple therapy in measures of effectiveness.

Dual therapy was inferior to triple therapy in one regard—among the sub-group of participants who entered the study having less than 200 CD4+ cells.

Changes in CD4+ cell counts

Below are the increased numbers of CD4+ cells that were reported for participants at different time points in the study:

48 weeks
- dual therapy – 197 more cells/ml
- triple therapy – 193 more cells/ml

96 weeks
- dual therapy – 267 more cells/ml
- triple therapy – 266 more cells/ml

Sub-group analyses

An average figure for viral load or CD4+ count at the start of therapy tends to smooth over differences in a large group where people have varying cell counts and viral loads. Thus, sub-group analyses—which look at sub-groups of people who have low CD4+ counts or high viral loads and analyses trends within these groups—are important. Below are some of these sub-group analyses.

The CD4+ count that some participants had at the start of the study (baseline) appeared to influence their subsequent response to the study regimens. For instance, there were 123 participants whose CD4+ count at the start of the study was less than 200 cells/ml. Below are the proportions whose treatment failed:
- dual therapy – 39%
- triple therapy – 21%

In contrast, among 682 participants who entered the study with a CD4+ count greater than 200 cells/ml, below is how their treatment failures were distributed:
- dual therapy – 14%
- triple therapy – 12%

Rates of treatment failure among 275 participants who had a baseline viral load greater than 100,000 copies/ml were distributed as follows:
- dual therapy – 36%
- triple therapy – 27%

Rates of treatment failure among participants whose baseline viral load was less than 100,000 copies/ml were distributed as follows:
- dual therapy – 7%
- triple therapy – 7%

At the start of the study about 5% of participants had a viral load greater than 500,000 copies/ml.

Among participants whose dual therapy regimens failed, four of five entered the study with a viral load “much greater” than 500,000 copies/ml. Analysis of their blood samples after treatment failure occurred found that in four of these five participants, HIV with mutations that allowed it to resist the effect of integrase inhibitors—the class to which raltegravir belongs—was present.

Safety and tolerability

None of the safety differences between study regimens were statistically significant.

Serious adverse events (SAEs)—these could be side effects, complications related to HIV or other causes—are always recorded in a clinical trial and then later analysed to determine if the study drugs played any role in their formation.

Here is the overall distribution of SAEs:
- dual therapy – 89 events were reported from 79 participants
- triple therapy – 75 events were reported from 61 participants
Death and other serious events

Here is the distribution of deaths that occurred during the study:

- dual therapy – four participants died; one death each from lymphoma, a severe drug hypersensitivity reaction, skin cancer, suicide
- triple therapy – one participant died from overdose of morphine

Very serious events were distributed as follows:

- dual therapy – eight cases in total, distributed as follows: elevated levels of enzymes in the blood suggestive of muscle breakdown (five cases); one each of liver inflammation, inflammation of the pancreas gland and Hodgkin’s lymphoma
- triple therapy – four cases in total, distributed as follows: elevated levels of enzymes in the blood suggestive of muscle breakdown (two cases); one heart attack and one case of elevated liver enzymes

Less than 1% of participants taking either study regimen had abnormal changes in fatty substances in the blood—cholesterol and triglycerides. Overall, there were no significant differences between regimens in the important ratio of total cholesterol to HDL-cholesterol.

Focus on the kidneys

There was a small but statistically significant decrease in kidney health (as assessed by using eGFR—estimated glomerular filtration rate) among triple-therapy users: eGFR increased by about 4 units. This is in contrast to an increase of 1 unit in eGFR seen among participants taking dual therapy.

These clinically insignificant changes were maintained for 96 weeks and underscore the overall safety of both study regimens for the kidneys.

Overall

According to the study researchers, a regimen of twice-daily raltegravir together with once-daily boosted darunavir was “well-tolerated” and had similar effectiveness as triple therapy with boosted darunavir. However, among participants who entered the study with less than 200 cells/ml, dual therapy with boosted darunavir and raltegravir was inferior to triple therapy.

Overall, the researchers found the safety of both regimens to be similar. They concluded by stating that the combination of raltegravir + boosted darunavir represents an alternative option (to boosted darunavir + Truvada) for first-line therapy, particularly in patients who have more than 200 CD4+ cells/ml.

Bear in mind

Although the results from NEAT are interesting, it is important to note that leading treatment guidelines, such as ones produced by the DHHS, do not recommend initiating HIV with simplified regimens.

REFERENCE:

B. Comparing the tolerability and effectiveness of initial therapy

Commonly used combinations for initial therapy of HIV can include the following:

- atazanavir (Reyataz) + low-dose ritonavir (Norvir) + Truvada (tenofovir + FTC)
- raltegravir (Isentress) + Truvada
- darunavir (Prezista) + low-dose ritonavir + Truvada

Researchers across the U.S. conducted a large study to compare the effects of these three regimens. They randomly assigned participants to receive one of the three regimens and monitored them for at least 96 weeks. As there were nearly 600 participants per regimen, the study was statistically robust and could determine if the regimens were equivalent, inferior or superior to each other.

Researchers concluded that, overall, each of the study regimens had equivalent virologic effectiveness. The atazanavir-containing regimen was not tolerated as well as the other two regimens. When researchers sought to analyse and compare each of the regimens for their combined
effectiveness and tolerability, a raltegravir-based regimen was superior to the other two. Furthermore, a regimen of boosted darunavir was superior to that of boosted atazanavir when assessed by the combined endpoint of tolerability and effectiveness.

Study details
Researchers recruited 1,808 HIV-positive participants and assigned them as follows:

- boosted atazanavir-containing regimen – 605 people
- raltegravir-containing regimen – 603 people
- boosted darunavir-containing regimen – 601 people

The average profile of participants at the start of the study was as follows:

- 76% men, 24% women
- age – 37 years
- HIV viral load – 40,000 copies/ml
- distribution of viral loads: 70% of participants had less than 100,000 copies/ml; 23% had between 100,000 to 500,000 copies/ml; 7% had more than 500,000 copies/ml
- CD4+ count – 308 cells/ml
- 30% of participants had less than 200 CD4+ cells/ml

Results—Week 96
Rates of virologic failure were similar when comparing all three regimens and were distributed as follows:

- boosted atazanavir-containing regimen – 13%
- raltegravir-containing regimen – 10%
- boosted darunavir-containing regimen – 15%

Statistical analysis found that all three regimens were equally effective at suppressing HIV.

According to researchers, virologic failure accompanied by detectable resistance was “rare” and distributed as follows:

- boosted atazanavir-containing regimen – 2%
- raltegravir-containing regimen – 3%
- boosted darunavir-containing regimen – less than 1%

Another way to assess the results was to compare the proportion of participants who were still on their assigned regimens at week 96 and whose viral load was less than 50 copies/ml:

- boosted atazanavir-containing regimen – 63%
- raltegravir-containing regimen – 80%
- boosted darunavir-containing regimen – 73%

The lower figure for participants taking atazanavir were driven by participants who were originally assigned atazanavir and later changed their regimen, mostly due to toxicity.

Tolerability
The proportion of participants in each regimen who developed side effects that they found intolerable and therefore quit their regimen was distributed as follows:

- boosted atazanavir-containing regimen – 16%
- raltegravir-containing regimen – 1%
- boosted darunavir-containing regimen – 5%

Based on these tolerability results, statistical tests revealed the following:

- the raltegravir-containing regimen was superior to the atazanavir-based regimen
- the raltegravir-containing regimen was equivalent to the darunavir-based regimen
- the darunavir-containing regimen was superior to the atazanavir-based regimen

A combined analysis
Prior to the start of the study, researchers had developed what they called a composite endpoint—essentially this was assessing the regimens due to cumulative failures caused by tolerability or detectable viral load. Using this composite endpoint, statistical analysis revealed the following:

- the raltegravir-containing regimen was superior to the boosted-darunavir or boosted-atazanavir regimen
- the boosted-darunavir regimen was superior to boosted atazanavir

These findings were driven by the tolerability issues among atazanavir users. Specifically, the most common reason for participants to discontinue taking atazanavir was because of severe or very severe yellowing of the skin and whites of the eyes (jaundice). This was due to an increase in the waste product bilirubin in their blood, caused
by atazanavir. This increase in bilirubin, called hyperbilirubinemia, is not harmful but can be annoying for some people.

Changes in CD4+ counts
At the 96-week mark, here are the increased number of CD4+ cells/ml that were distributed by regimen:
- boosted atazanavir-containing regimen – 284 more cells/ml
- raltegravir-containing regimen – 288 more cells/ml
- boosted darunavir-containing regimen – 256 more cells/ml

These differences are not clinically meaningful.

The researchers affiliated with this study made the following conclusions:
- All three regimens are virologically equivalent.
- Boosted atazanavir is not as well tolerated as the other regimens.
- Raltegravir was superior to the other regimens when taking into account its tolerability and antiviral activity.
- Boosted darunavir was superior to boosted atazanavir when taking into account its tolerability and antiviral activity.

It is not over
Further analyses of the data from this study are underway. Such sub-studies will yield information about the impact of different treatments on the following (or in some cases, vice versa):
- cardiovascular health
- metabolic issues
- bone density
- inflammation
- adherence
- gender

REFERENCE:

C. Different strains of HIV
HIV can be divided into two main groups of viruses, as follows:
- HIV-1
- HIV-2

HIV-1 is the most common form of the virus and is found throughout the world. HIV-2 is most commonly found in West Africa but is being gradually displaced by HIV-1. This short report focuses on HIV-1 and its diversity.

HIV-1 can be subdivided into at least nine major strains, or subtypes, as follows:

All of these subtypes are classed as group M (or main) by virologists.

In North America, Western Europe, Australia and Japan, the most common subtype of HIV-1 is subtype B.

There are also six sub-subtypes of HIV-1, as follows:
- A₁ to A₄, F₁ to F₂

There is another group of HIV called group O (outlier).

There are also many circulating recombinant forms (CRFs), at least 48 of them, such as the following:
- AE, AB, BC

Due to travel, tourism and immigration, other strains and CRFs have been appearing in these countries and regions.

When a doctor submits a patient’s blood sample for genotypic resistance testing in Canada, the analysis that is sent from the lab to the doctor’s office lists the clade, or subtype, to which the patient’s virus belongs.

Subtypes of HIV may be an issue for the emerging class of therapies called attachment inhibitors, as we explain in the next report.

REFERENCES:


D. Attachment inhibitor shows some progress

Programs that have sought to develop anti-HIV drugs (of all classes) have sometimes produced candidate compounds that may appear potent in laboratory experiments with cells. However, when these compounds are later tested in people, they sometimes fail to make it through phase I, II or III clinical trials, often because of toxicity or insufficient effectiveness.

Leading treatment guidelines in high-income countries today generally encourage the use of drugs for the initial therapy of HIV, which, in most cases, are not the first member of their class that were developed. This is particularly the case for commonly used classes of HIV medicines—nukes, non-nukes and protease inhibitors.

Looking at drug classes

Looking within the class of drugs called protease inhibitors, initial treatments included saquinavir (Invirase), high-dose ritonavir (Norvir) and indinavir (Crixivan). Today the U.S. Department of Health and Human Services (DHHS) guidelines—the most comprehensive of HIV treatment guidelines—largely prefer that doctors, if they chose to prescribe protease inhibitors, prescribe darunavir (Prezista) or atazanavir (Reyataz), both accompanied with a small dose of ritonavir. The purpose of the small dose of ritonavir is to raise, or boost, the concentration of the other protease inhibitor in the blood so that once-daily dosing is possible.

Within a drug development program, the candidate compound that finally enters phase III clinical trials is probably one of several that were developed, with the earlier versions discarded because of insufficient potency or other issues. This was the case with the pharmaceutical company Merck and its integrase inhibitor program. Although Merck scientists were searching for and creating integrase inhibitors in the early 1990s, it was only in 2007 that one integrase inhibitor, raltegravir (Isentress), successfully completed all three main phases of clinical trials to ensure that it was licensed by regulatory agencies.

Enter the attachment inhibitor

For the past decade, researchers at the Bristol-Myers Squibb Corporation (BMS) have been developing a new class of anti-HIV compounds called attachment inhibitors. These drugs work by interfering with a viral protein called gp120. By binding to this protein, attachment inhibitors prevent HIV from attaching to and entering and infecting a cell.

BMS has produced several attachment inhibitors but has encountered difficulties with early candidate compounds. One of the difficulties is that candidate compounds work well in lab experiments with cells and HIV. However, initial studies in people did not yield promising results. In particular, it seemed that early candidate attachment inhibitors were not well absorbed.

To help overcome this important barrier, scientists at BMS have developed a new formulation of their latest attachment inhibitor using a prodrug, an idea explained below.

About prodrugs

BMS has a drug with the interim name BMS-663068. When this drug is swallowed and reaches the intestine, enzymes there convert it into another drug called BMS-626529 (which we shorten to '529). This latter drug, '529, is the one with active anti-HIV activity. Drugs that are taken in one form and then converted in the body into their active form are called prodrugs.

A short clinical trial with BMS-663068 as a single agent for at least eight days in HIV-positive volunteers has found that viral load fell between 1.2 and 1.7 logs.

Not everyone who took this drug had large decreases in viral load. BMS scientists were able to determine the reasons for this in five of six non-responders. It seems that HIV isolated from these five people was not susceptible to the attachment inhibitor. It appears that some strains of HIV have pre-existing, naturally occurring mutations to attachment inhibitors. These mutations allow these strains of HIV to resist the effects of attachment inhibitors.
Where are the mutations?

Studying attachment inhibitors and possible resistance mutations associated with them is an emerging field, so findings in this area are evolving. However, resistance to the BMS attachment inhibitor is not common in the strain of HIV that is widely found in North America, Western Europe, Australia and Japan—subtype B. Rather, strains of HIV belonging to subtypes AE and Group O seem to have some naturally occurring, pre-existing resistance mutations to the BMS attachment inhibitors.

Study details

In the latest clinical trial for which we have details, researchers working with BMS-663068 enrolled 250 participants. During the screening process for the trial, all participants underwent tests to have their HIV analysed to be sure that it would respond to the attachment inhibitor. After successful screening, all participants were assigned to receive the following drugs:

- raltegravir (Isentress) + tenofovir (Viread)

In addition, they were randomly assigned to receive one of four doses and schedules of BMS-663068, ranging from 400 mg twice daily to 1,200 mg once daily.

For purposes of comparison, one group of participants received the following regimen:

- raltegravir + tenofovir (Viread) + atazanavir + low-dose ritonavir

The average profile of participants at the start of the study was as follows:

- 60% male, 40% women
- age – 40 years
- HIV strains – most participants (67%) had subtype B, but some participants had subtype C and other strains
- HIV viral load – 63,000 copies/ml
- 45% of participants had a viral load greater than 100,000 copies/ml
- CD4+ count – 250 cells/ml
- 40% of participants had a CD4+ count less than 200 cells/ml

Many participants had experienced the failure of their first and second regimens prior to enrollment.

For the first part of the study, lasting about a week, participants underwent monotherapy with the attachment inhibitor. After this they took combination therapy as outlined earlier.

Results—Monotherapy

Viral load fell depending on the dose of the attachment inhibitor used. For instance, among participants who took 400 mg twice daily, it fell an average of 0.69 log; among participants who took 1,200 mg once daily it fell by about 1.5 log.

Results—After 24 weeks of combination therapy

Here are the proportions of participants who had a viral load less than 50 copies/ml in each of the different combination therapies. Although all participants received combination therapy, because the drug of importance is the attachment inhibitor, we focus on the dose of that drug here:

- 400 mg twice daily – 80% had a viral load less than 50 copies/ml
- 800 mg twice daily – 69% had a viral load less than 50 copies/ml
- 600 mg once daily – 77% had a viral load less than 50 copies/ml
- 1,200 mg once daily – 72% had a viral load less than 50 copies/ml

For comparison, among participants who took a regimen of already approved drugs (raltegravir + tenofovir + atazanavir + ritonavir), 75% had a viral load below the 50-copy/ml mark at week 24.

Increases in CD4+ counts were similar among all participants—about 120 more CD4+ cells/ml by week 24.

Based on the effectiveness of the 1,200 mg dose, particularly in monotherapy, partway through the study BMS decided to have all participants take a 1,200 mg once-daily dose of the attachment inhibitor.

Safety

Doctors involved with the study could not find any side effects caused by the attachment inhibitor. Four participants left the study prematurely, for
reasons unrelated to exposure to the attachment inhibitor, as follows:

• one case of abnormal heart rhythms in a person who injected street drugs
• two cases of TB (some participants were recruited from countries where tuberculosis is relatively common)
• one case of severe kidney injury caused by exposure to tenofovir

Among people taking the regimen of already approved drugs, moderate-to-severe episodes of nausea, diarrhea and vomiting were reported.

Screening

Prior to enrollment, as part of the screening process, only 5% of volunteers were excluded from the study because their virus was not susceptible to the attachment inhibitor. Until larger studies are done, it is not clear what role pre-screening people for susceptibility to the attachment inhibitor will have. For instance, BMS '068 has been designed for treatment-experienced patients, many of whom will also likely be taking ritonavir-boosted protease inhibitors. Ritonavir can also boost levels of the attachment inhibitor. BMS researchers suggest that these increased levels of the attachment inhibitor carry the possibility, at least in theory, of overcoming any naturally occurring resistance some strains of HIV might have to the attachment inhibitor.

Looking ahead

BMS researchers plan to continue monitoring participants taking the attachment inhibitor for 48 weeks, perhaps longer. If this phase II study shows prolonged effectiveness of the attachment inhibitor and no problems emerge, then phase III trials are likely in the future.

Laboratory experiments suggest that if HIV does develop resistance to one attachment inhibitor, it likely remains susceptible to other experimental attachment inhibitors.

REFERENCES:


II HEPATITIS C VIRUS

A. More surprises ahead for hepatitis C therapy

Just a few years ago the standard treatment for hepatitis C virus (HCV) infection in Canada and other high-income countries was a combination of long-lasting interferon (called peginterferon) and the nucleoside analogue (nuke) ribavirin. Both drugs have tolerability issues. Interferon can cause muscle aches, bone pains, fatigue, irritability, anxiety and depression. Ribavirin can cause severe
fatigue, itchy skin and can affect the health of the bone marrow. Furthermore, treatment with these drugs usually cured only about 50% of people infected with HCV alone. Rates of recovery among people co-infected with HCV and HIV were much lower.

Both interferon and ribavirin attack HCV indirectly and also help the immune system in its effort to overcome this virus.

**Direct Acting Agents (DAAs)**

About 10 years ago, researchers with the pharmaceutical company Boehringer-Ingelheim in Quebec discovered and began to develop a novel therapy for HCV. This drug was given the interim designation BILN 2061. It could reduce levels of HCV in the blood and worked by interfering with an enzyme needed by HCV-infected cells, called NS3 protease. In other words, this drug was the first HCV protease inhibitor to enter clinical trials. However, while initial results with BILN 2061 were promising, development of this drug was halted due to cardiac toxicity in animals and the worry that the same side effect could occur in people. BILN 2061 was an example of a drug that attacked HCV directly. Such designer drugs are called Direct Acting Agents (DAAs).

Since that time, particularly in the past three years, progress in HCV drug development has moved rapidly. The first wave of HCV protease inhibitors approved in high-income countries were meant to be used as part of the following regimens:

- boceprevir (Victrelis) + peginterferon + ribavirin
- telaprevir (Incivek) + peginterferon + ribavirin

These protease inhibitors, when used as part of combination therapy, generally increased recovery rates to between 65% and 75%. However, they were mainly designed to treat one strain (or genotype) of HCV called genotype 1 (GT1). Moreover, the protease inhibitors had to be taken several times a day, and telaprevir had to be taken with fat. In some cases, prolonged therapy was required. These drugs also had side effects and drug interactions, some of which could be dangerous. A major weakness of both drugs is that their effectiveness relied heavily upon interferon and ribavirin.

In December 2013, two new HCV drugs were licensed for use in Canada:
- sofosbuvir (a nucleotide analogue) made by Gilead Sciences
- simeprevir (a protease inhibitor) made by Janssen

Sofosbuvir has to be used in combination with ribavirin, and sometimes both ribavirin and peginterferon, depending on the genotype of HCV that is being targeted. Simeprevir has to be used with both peginterferon and ribavirin. Both simeprevir and sofosbuvir can be taken once daily without food requirements. Courses of treatment will vary between 12 and 24 weeks, depending on factors such as the strain of HCV and the combination of drugs used. Cure rates can reach between 75% and 100%.

In just four years, that is enormous progress: from 48 weeks down to 12 weeks of therapy and very high rates of recovery.

**Emerging therapies**

Both sofosbuvir and simeprevir are being tested in clinical trials in combination with each other and with other drugs, in many cases without the addition of ribavirin or interferon.

Other leading contenders are combinations of drugs being developed by pharmaceutical companies Abbvie and Bristol-Myers Squibb. Thus, perhaps three years from now, it is possible that the choice for initial treatment of HCV, particularly the most common strains found in high-income countries, will be interferon-free regimens. Moreover, newer combinations of DAAs may be even more potent, achieving cure rates of 99% or greater.

Five years from now there may still be a role for peginterferon, though this will probably be restricted to cases where first- and second-line therapies have failed.

**Moving away from ribavirin**

Many potential users of HCV treatment have concerns about interferon; this is reasonable because of the potential side effects previously mentioned. But as interferon becomes less necessary, another element of HCV treatment regimens comes under scrutiny—ribavirin. Historically, exposure to this drug is generally
linked to anemia and fatigue. As more powerful DAAs emerge, more researchers are comparing ribavirin-containing and ribavirin-free regimens. In general, these emerging DAAs have few side effects compared to interferon- and ribavirin-based regimens. Furthermore, as interferon is gradually being supplanted in regimens with new DAAs, it is becoming clear that ribavirin causes a wide range of unpleasant side effects. Hopefully, future regimens will be sufficiently potent to exclude ribavirin.

**Shrinking time**

A further indicator of progress is that scientists at the U.S. National Institutes of Health (NIH) recently announced preliminary results from an experimental combination of drugs that suggested only six consecutive weeks of therapy may be needed to cure some cases of HCV, provided the combination of DAAs was sufficiently potent. As we mentioned, the results are still preliminary and relatively small numbers of participants were enrolled but this direction suggests a promising trend. Dutch virologist Charles Boucher, PhD, has suggested that even shorter regimens—just four weeks—be tested for their effectiveness.

The field of HCV therapy promises to be exciting for many years as doctors working with available regimens try to answer at least the following questions:

- Which combination of drugs is the most powerful?
- Which combination of drugs is the safest?

As each year passes, it seems that more is being demanded of emerging HCV regimens.

**The barrier of cost**

For the majority of people with HCV infection, therapy is expensive. Most HCV-positive people in high-income countries are able to access therapy either because they have private insurance coverage or they can have therapy subsidized by regional authorities. The listed prices for DAAs are not trivial and so regional health authorities need to negotiate a reasonable discount from manufacturers, as they have done for therapies for cancer, HIV and other catastrophic illnesses. In the absence of a large discount, it is likely that rationing of HCV therapy may become necessary. If a large discount from manufacturers is obtained, health authorities can then begin to plan campaigns where the offer of HCV testing is made followed by counselling and swift referral for HCV treatment in cases where infection has been confirmed.

**HIV co-infection**

In this issue of TreatmentUpdate, we cover leading combinations of HCV drugs mainly used for the treatment of HCV mono-infection. However, as more powerful anti-HCV drugs are developed and licensed, leading hepatologists, gastroenterologists and infectious disease specialists increasingly think it is likely that the same combinations used by HCV mono-infected people can be used by people co-infected with HCV and HIV.

**Resources**

Here are some links to important background information about HCV drugs and their effectiveness:

**Classifying different HCV drugs**

**Understanding SVR<sub>12</sub> vs SVR<sub>24</sub>**

**REFERENCES:**


B. Abbvie’s potent combination

Abbvie (formerly Abbott Laboratories) is developing many drugs for the treatment of HCV. The corporation’s first generation of drugs consists of the following agents:

- **ABT-450** interferes with the HCV proteins NS3/4A and it is taken once daily with a small dose (100 mg) of another drug called ritonavir (Norvir). The purpose of the small dose of ritonavir is to boost and maintain levels of ABT-450 in the blood. Ritonavir does not have activity against HCV and has only minimal activity against HIV at such a low dose.

- **ABT-267** (ombitasvir) interferes with the HCV protein NS5A and is taken once daily.

- **ABT-333** (dasabuvir) interferes with the HCV protein NS5B and is taken twice daily.

ABT-450, 267 and 333 are examples of DAAs (direct-acting antiviral agents).

Many clinical trials of these drugs have taken place. One of the latest studies whose results were released is called Pearl-III. This study was a phase III trial of the drugs mentioned above with or without the nuke ribavirin in participants who had not previously been treated and who did not have severe liver injury (cirrhosis). All participants had HCV genotype 1b.

Preliminary results from Pearl-III suggest that the combination of three DAAs being developed by Abbvie is extremely powerful, resulting in very high cure rates of about 99%. Furthermore, the combination appears to be as effective with or without ribavirin. Also, the combination of three DAAs appears to be safer than regimens containing ribavirin.

The Pearl-III study is important for other reasons. Historically, many of the problems associated with HCV treatment were blamed on exposure to interferon. However, the Pearl-III study was interferon-free and compared two regimens, one containing ribavirin and the other without ribavirin. The rate of side effects in Pearl-III was greater among ribavirin users.

**Study details**

A total of 419 participants were randomized to receive one of the following regimens:

- 3 DAAs + ribavirin – 210 participants
- 3 DAAs + fake ribavirin (placebo) – 209 participants

Although participants will only have been exposed to the study drugs for 12 weeks, researchers plan to monitor them for 60 weeks.

The doses of medicines were as follows:

- **ABT-450** – 150 mg
- ritonavir – 100 mg
- **ABT-267** – 25 mg

All of the three drugs listed above were co-formulated (put into one pill) and taken once daily.

The dose of ABT-333 was 250 mg twice daily.

The dose of ribavirin was as follows:

- for people who weighed less than 75 kg – 1,000 mg per day
- for people who weighed 75 kg or more – 1,200 mg per day

The average profile of participants at the start of the study was as follows:

- similar proportions of men and women
- age – 49 years
- most participants (70%) had minimal liver injury
- 20% had a moderate amount of liver injury
- 10% had extensive liver injury
- HCV viral load – 2 million copies
Results

• among participants who received three DAAs + ribavirin – 99.5% (209 out of 210) had no detectable viral load at the 12th week of therapy (SVR<sub>12</sub>)
• among participants who received three DAAs + placebo, 99% (207 out of 209) had no detectable viral load at the 12th week of therapy (SVR<sub>12</sub>)

This difference between the two regimens suggests that a ribavirin-free regimen of three DAAs was statistically no worse than three DAAs + ribavirin (the technical term for this is “non-inferior”).

Comparing both combinations to historical results based on the current standard of care—telaprevir + interferon + ribavirin (assuming that this historical regimen resulted in a 75% cure rate)—found that both regimens, three DAAs with and without ribavirin, were statistically superior.

Three participants in the current study did not develop SVR<sub>12</sub> for the following reasons:

• one participant taking three DAAs + ribavirin experienced treatment failure
• two participants in the ribavirin-free arm stopped returning to the study clinic; one of them developed undetectable HCV at week 4 of the study

There was no impact of race, gender or genetics on the response to therapy.

Adverse events

Researchers must note all adverse events that occur in a study to later analyse them and determine if they were caused by the medications used. Here are some adverse reactions reported:

Headache (generally of mild intensity)
• 24% with both study regimens

Fatigue
• 22% with both study regimens

Differences in adverse events emerged as follows:

Itchy skin
• 3 DAAs + ribavirin – 12% of participants
• 3 DAAs – 5%

Nausea
• 3 DAAs + ribavirin – 11%
• 3 DAAs – 4%

Weakness
• 3 DAAs + ribavirin – 11%
• 3 DAAs – 5%

Difficulty falling asleep
• 3 DAAs + ribavirin – 9%
• 3 DAAs – 3%

Cough
• 3 DAAs + ribavirin – 9%
• 3 DAAs – 2%

Serious adverse events (SAE) occurred in four participants on each regimen. However, only one SAE—a case of arthritis—appeared to be linked to exposure to the three DAAs.

Differences in lab tests were distributed among the regimens’ users as follows:

Anemia
• 3 DAAs + ribavirin – 7%
• 3 DAAs – 1%

Hemoglobin (a protein that helps to transport oxygen to tissues) levels less than 10 grams per dL
• 3 DAAs + ribavirin – 9%
• 3 DAAs – 0%

The dose of ribavirin had to be decreased in 19 out of 210 people (9%) because of anemia and other problems. However, all were still able to recover from HCV.

Bilirubin (a waste product; elevated levels of which can temporarily discolour the skin and whites of the eyes) levels more than three times the upper limit of normal:
• 3 DAAs + ribavirin – 6%
• 3 DAAs – 1%

ALT (alanine aminotransferase; a liver enzyme) levels greater than five times the upper limit of normal
• 3 DAAs + ribavirin – 1%
• 3 DAAs – 0%

AST (aspartate aminotransferase; a liver enzyme) levels greater than five times the upper limit of normal
• 3 DAAs + ribavirin – 0%
• 3 DAAs – 0%

The results from Pearl-III are compelling and show that a regimen of the three Abbvie DAAs is very powerful and generally safe. Furthermore, it appears that in some patients with only a small degree of liver injury, ribavirin is not necessary
when used with the three DAAs in this study. Further studies of these drugs will be featured in a future issue of TreatmentUpdate.

Abbvie is developing its second-generation anti-HCV therapy whereby the company hopes to simplify a regimen to one pill, once daily, perhaps without ritonavir boosting. However, it will be several years before we will know if such a regimen can work in large numbers of participants.

REFERENCE:

C. Simeprevir – potential drug interactions

In December 2013, Health Canada approved the sale and use of a new anti-HCV drug called simeprevir. This drug is sold under the brand name Galexos and is made by the Janssen company.

Simeprevir belongs to a class of drugs called HCV protease inhibitors. It is meant to be used as part of combination therapy with peginterferon and ribavirin. However, at least one clinical trial has found that the combination of simeprevir and sofosbuvir is potent, highly effective and safe, so some doctors may prescribe it in cases where patients have private insurance coverage that will pay for it. Until simeprevir is listed on provincial and territorial formularies, it is not clear if provinces and territories will pay for this combination.

Simeprevir is available in capsules of 150 mg and the dose is one capsule once daily. This drug does not have food or water restrictions. Simeprevir was relatively well tolerated in clinical trials and most side effects reported were of mild-to-moderate intensity. Common side effects in these clinical trials included the following:

- rash
- itchy skin
- higher-than-normal levels of the waste product bilirubin in the blood
- sensitivity to sunlight

Drug interactions

Drugs can influence the absorption of and the body’s ability to break down other drugs. This effect of one drug on another drug(s) is called a drug interaction. Such interactions can result in intensified side effects, new side effects or the loss of effectiveness. Always speak to your nurse and doctors(s) about the medicines that you are taking, particularly your specialist(s) and family doctor. Tell them about any over-the-counter drugs you are taking, as well as any herbs or supplements. Pharmacists can be an especially helpful source of information about drug interactions.

The list of interactions

Below is a list of actual and potential interactions that may occur with simeprevir. Please note that this list is not exhaustive. We also provide recommendations by Janssen about how to deal with some potential interactions for simeprevir users. It is important that any changes to the drugs that you are taking be made by your physician(s) to maximize your chances of recovery from HCV and minimize any risk of harm.

Here is the list of actual and potential interactions that may occur with simeprevir:

Drugs for abnormal heart rhythms
- Digoxin – simeprevir can raise the level of digoxin in your body. Your doctor will need to monitor the amount of digoxin in your blood and perhaps adjust your dose.
- Other drugs for abnormal heart rhythms: amiodarone, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine – simeprevir can raise the level of these drugs. The manufacturer recommends that they be used cautiously and advises that their level in your blood requires monitoring.

Antiseizure drugs
- Including carbamazepine, oxcarbazepine, phenobarbital, phenytoin – all of these drugs can significantly reduce the amount of simeprevir in your blood. Ask your doctor for a different anti-seizure medication, as the manufacturer recommends that simeprevir should not be used with these drugs.

Antihistamines
- Simeprevir can raise the amount of astemizole and terfenadine and Janssen recommends that they not be used.
Antibiotics – general
• Clarithromycin, erythromycin and telithromycin raise levels of simeprevir. Erythromycin should not be taken by patients who are prescribed simeprevir. Janssen suggests that doctors consider an alternative antibiotic, azithromycin.

Antibiotics – TB
• Rifampin, rifabutin and rifapentene should not be used because they significantly reduce the amount of simeprevir in the body.

Antifungal drugs
• Itraconazole, ketoconazole, posaconazole and voriconazole all raise simeprevir levels and Janssen recommends that they not be used.

Calcium channel blockers
• Amlodipine, bepridil, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil – simeprevir can raise the levels of these drugs. Janssen states that they be used cautiously and that “clinical monitoring of patients is recommended.”

Cholesterol medicines
• Statins, including atorvastatin, lovastatin, pitavastatin, rosuvastatin and simvastatin – simeprevir can raise the levels of these drugs in your body. Janssen recommends starting with the lowest “necessary” dose of these medicines when taking simeprevir.

Corticosteroids (oral or intravenous)
• Dexamethasone – as this drug can reduce simeprevir levels, it should not be used by patients taking simeprevir.

GI drugs
• Prepulsid, Propulsid (cisapride) – this should not be used as it may cause abnormal heart rhythms.

Herbs
• St John’s wort (hypericin, hyperforin), milk thistle – these herbs should not be used by people taking simeprevir, as St. John’s wort can reduce the amount of simeprevir in the body and milk thistle can raise the amount of simeprevir in the body.

HIV drugs
• Non-nukes: efavirenz (Sustiva, Stocrin and in Atripla), delavirdine (Rescriptor), etravirine (Intolerance and in Complera) and nevirapine (Viramune) – these drugs should not be used by patients who take simeprevir, as they can lower the concentration of simeprevir or vice versa.
• Protease inhibitors: including atazanavir, cobicistat (in Stribild), darunavir, fosamprenavir, indinavir, lopinavir (Kaletra), ritonavir (Norvir and in Kaletra), saquinavir, tipranavir – these drugs can have significant interactions with simeprevir. They can raise simeprevir levels and vice versa. Janssen recommends that people taking simeprevir do not take these protease inhibitors. If you are taking an HIV protease inhibitor and plan to use simeprevir, speak to your doctor about changing your HIV therapy.
• Pulmonary Arterial Hypertension (PAH) drugs – sildenafil, tadalafil and vardenafil are used for the treatment of PAH. Janssen recommends that patients start with the lowest dose of these drugs and increase the dose under the close supervision of their doctor.
• Male sexual dysfunction drugs: sildenafil, tadalafil, vardenafil – speak to your doctor and pharmacist about the dose of these drugs that is right for you while you are taking simeprevir.
• Sedatives (sleeping pills) or anti-anxiety drugs – these drugs must be used cautiously, as simeprevir has the potential to raise their levels in the body, causing side effects. Speak to your doctor and pharmacist about what sedatives are safe for you to use while taking simeprevir. 
• Transplant medicines – simeprevir can raise levels of cyclosporine, lower levels of tacrolimus or do both to sirolimus. Therefore, monitoring of transplant drugs while you are taking simeprevir is necessary.

REFERENCE:
D. Simeprevir in HIV co-infection

In clinical trials, about 80% of participants treated with simeprevir have been cured of HCV. These trials have largely recruited people with HCV infection alone (mono-infection). Due to shared routes of transmission, some HCV-positive people are also infected with HIV (co-infection) and they also require HCV treatment.

Researchers conducted a study called C212 where 106 HCV-HIV co-infected volunteers were recruited and underwent assessments of liver injury and other health issues. Each participant’s HCV treatment history was reviewed and depending on their treatment history they were assigned to one of two regimens described below.

People who had never been previously treated for HCV or who were classed as relapers because of their response to prior HCV treatment received the following regimen:

- simeprevir + PR (peginterferon + ribavirin) for 12 weeks. After this time simeprevir was stopped and therapy with PR continued for 12 more weeks and then stopped. Then participants continued to be monitored for 24 weeks.

People who doctors classified as “prior relapers, prior partial responders, prior null responders” or who had severe liver injury due to HCV (cirrhosis) were assigned the following regimen:

- simeprevir + PR (peginterferon + ribavirin) for 12 weeks. After this time simeprevir was stopped and therapy with PR continued for 36 more weeks. Then participants were monitored for 24 weeks.

Participants were not allowed to use HIV protease inhibitors because of possible drug interactions. Instead, they were allowed to take a regimen using drugs from the following categories:

- nukes – 3TC, FTC, tenofovir, abacavir
- non-nukes – rilpivirine (Edurant and in Complera)
- integrase inhibitors – raltegravir
- fusion inhibitor – T20 (Fuzeon)
- co-receptor blockers – maraviroc

Furthermore, during the study, researchers did not allow the use of experimental therapies.

The average profile of participants at the start of the study was as follows:

- 85% men, 15% women
- age – 48 years
- 27% had genes associated with a favourable response to interferon
- HCV viral load – 10 million copies/ml
- 82% of participants had the strain of HCV called genotype 1a
- 12% of participants had cirrhosis
- HIV viral load – 89% of participants had less than 50 copies/ml
- CD4+ count – 629 cells/ml

Results

At this time participants have not been monitored to the end of the study. However, data on the proportion of participants who have achieved undetectable HCV viral load for 12 consecutive weeks after the cessation of therapy (this period is called SVR12) is available.

Overall, 74% of participants had an SVR12 and would be extremely likely to recover from HCV infection (further monitoring is ongoing to confirm this).

Recovery rates in different sub-groups of participants were as follows:

- no previous treatment – 79% recovered
- prior relapers – 87% recovered
- partial prior responders – 70%
- prior null responders – 57%

This is a dramatic improvement compared to just using interferon and ribavirin alone in historical trials (recovery rates in co-infection would be about 30%).

Among participants with a severe degree of liver injury (graded as F3 or F4), there was an overall recovery rate of 64%.

Among participants with different genotypes of HCV, recovery rates were as follows:

- Genotype 1b – 89% recovered
- Genotype 1a – 71% recovered
Results – HIV
Only two participants had their HIV viral load rise above the 50-copy/ml mark. However, in both cases this occurred 12 weeks after they left the study.

Results – Adverse events
Most side effects were due to exposure to peginterferon + ribavirin and included the following:

- fatigue – 41%
- nausea – 26%
- headache – 28%
- less-than-normal levels of neutrophils – 28%
- less-than-normal levels of red blood cells – 21% (in only two participants was this severe)
- itchy skin – 20%
- rash – 17%
- sensitivity to sunlight – 2%

These rates of side effects were generally similar to what is seen in people who have HCV infection alone and who have received treatment.

REFERENCE:

E. Simeprevir + interferon + ribavirin in HCV genotype 4 infection
HCV genotype 4 (GT4) is relatively common in the Middle East and Africa. Due to migration, travel and tourism, the number of people with GT4 is increasing in high-income countries.

Simeprevir has antiviral activity against HCV GT1 and has been licensed for treating this strain. Researchers have recently tested it as part of combination therapy in people with GT4, who were either new to HCV therapy or who had previously used peginterferon but without success.

Study details
Stopping rules – Doctors stopped therapy if blood tests confirmed a poor virologic response at any of the following points during the course of the study:

- Week 4 – HCV viral load was greater than 1,000 IU/ml
- Week 12 – HCV viral load was greater than 1,000 IU/ml
- Week 24 – HCV viral load was 25 IU/ml or greater
- Week 36 – HCV viral load was 25 IU/ml or greater

Participants were divided into two groups and assigned to receive the following regimens:

Group 1 – People who were new to HCV treatment or who had previously been treated with an initially favourable response but then relapsed:

- Simeprevir 150 mg once daily (for 12 weeks) + peginterferon + ribavirin; at week 24 if HCV RNA was less than 25 IU/ml, therapy stopped. If HCV RNA was greater than this amount, therapy with peginterferon and ribavirin continued for 24 more weeks.

Group 2 – People who had a prior poor response to HCV therapy:

- Simeprevir 150 mg once daily (for 12 weeks) + peginterferon + ribavirin (for a total of 48 weeks)

For this interim analysis, researchers analysed data from 107 participants distributed as follows:

- 35 participants who had not been treated previously
- 72 participants who were treatment experienced

Treatment-experienced participants could be further subdivided as follows:

- prior relapsers – 22 people
- prior partial responders – 10 people
- prior null responders – 40 people

The average profile of participants was as follows:

- 79% men, 21% women
- age – 50 years
- 72% were white, 28% were black
- HCV viral load – 6.1 log
• main subtypes of HCV GT4 were 4a and 4d; other subtypes included c, e, f, h, k, o, q, r
• most participants had a mild-to-moderate degree of liver damage

Results – Week 4

Having HCV that was less than 25 IU/ml at week 4 is called a rapid virologic response (RVR) and this occurred as follows:

Overall – 66%
• never previously used treatment – 80%
• prior relapsers – 90%
• prior partial responders – 40%
• prior null responders – 49%

As this is an interim analysis, not all the participants had completed the study when the data were analysed. However, out of all 30 participants who completed 24 weeks of therapy, 29 (97%) had a viral load less than 25 IU/ml.

Side effects

Most side effects were generally of mild-to-moderate intensity. Since all participants received interferon and ribavirin, side effects were common. However, only four participants had side effects that were considered serious by researchers and only one participant quit simeprevir because of side effects. No one died while in the study.

Common side effects in the first 12 weeks of the study (when simeprevir was used) were as follows:
• anemia – 8% (generally mild)
• less-than-normal levels of neutrophils – 5% (mostly mild-to-moderate)
• itchy skin – 19%
• rash – 13%
• higher-than-normal levels of bilirubin in the blood (2%)

Not enough patients have completed the study to draw firm conclusions about the effectiveness of this therapy. However, the interim results are very promising.

REFERENCE


F. Sofosbuvir in co-infection with different genotypes

Sofosbuvir is a nucleotide polymerase inhibitor taken at a dose of 400 mg once daily as part of combination therapy for HCV. When sofosbuvir is used with ribavirin, the dose of ribavirin is often adjusted based on a person’s weight.

In a clinical trial called Photon 1, researchers tested different schedules of sofosbuvir + ribavirin in people co-infected with different strains, or genotypes (GT), of HCV. Participants were divided into the following groups:
• no previous treatment and GT1 – 114 participants received treatment for 24 weeks
• no previous treatment and GT2 or 3 – 68 participants received treatment for 12 weeks
• prior unsuccessful treatment and GT2 or 3 – 41 participants received treatment for 24 weeks

The average profile of participants at the time they entered the study was as follows:
• 80% men, 20% women
• age – 50 years
• common HCV genotypes– GT1a, GT2 and GT3
• 95% of participants were taking ART
• CD4+ count – 600 cells/ml

Commonly used anti-HIV drugs included the following:
• efavirenz
• atazanavir + ritonavir
• darunavir + ritonavir
• raltegravir
• rilpivirine
• Truvada

Results

Between 90% and 98% of participants completed the study. Depending on their subgroup and strain of HCV, between 75% and 100% of participants recovered from HCV infection.

Specific results – GT1
The proportion of participants with an undetectable HCV viral load at different times was as follows:
• Week 4 – 96%
• end of treatment – 100%
• sustained virologic response (SVR$_{12}$) 12 weeks after the end of therapy – 76%
• sustained virologic response (SVR$_{24}$) 24 weeks after the end of therapy – 75%

Thus, 75% of participants with GT1 were cured.

**Specific results – GT2 (who had no previous treatment)**
The proportion of participants with an undetectable HCV viral load at different times was as follows:

• Week 4 – 96%
• end of treatment – 96%
• sustained virologic response (SVR$_{12}$) 12 weeks after the end of therapy – 88%
• sustained virologic response (SVR$_{24}$) 24 weeks after the end of therapy – 88%

Thus, 88% of participants with GT2 who had no prior therapy were cured.

**Specific results – GT2 who had prior unsuccessful therapy**
• Week 4 – 100%
• end of treatment – 100%
• sustained virologic response (SVR$_{12}$) 12 weeks after the end of therapy – 92%
• sustained virologic response (SVR$_{24}$) 24 weeks after the end of therapy – 92%

Thus, 92% of GT2 participants who had prior unsuccessful therapy were cured.

One participant became re-infected with HCV during the study.

**Specific results – GT3 (no prior therapy)**
The proportion of participants with an undetectable HCV viral load at different times was as follows:

• Week 4 – 100%
• end of treatment – 98%
• sustained virologic response (SVR$_{12}$) 12 weeks after the end of therapy – 67%
• sustained virologic response (SVR$_{24}$) 24 weeks after the end of therapy – 67%

Thus, 67% of participants with GT3 who had no prior therapy were cured.

**Specific results – GT3 who had unsuccessful prior therapy**
• Week 4 – 100%
• end of treatment – 100%

This study is not the final word on treatment for co-infection, but Photon 1 does show that interferon-free regimens can result in relatively high rates of cure in co-infected people. More potent regimens are needed because there were relatively high rates of relapse among some participants with genotypes 1 (25 participants) and 3 (12 participants).

Technicians analysed blood samples and did not find HCV that was resistant to sofosbuvir.

**Adverse events**

Common side effects were reported by the following proportion of participants:

• fatigue – 35–40%
• difficulty falling asleep – 15–21%
• nausea – 15–18%
• headache – 14%
• irritability – 10%
• diarrhea – 10%
In seven cases, participants stopped taking their study drugs for the following reasons:

- persistent weight loss
- difficulty falling asleep and feeling agitated
- attempted suicide
- persistent sensation of foreign object lodged in throat
- increased feelings of anxiety
- shortness of breath

One person died nine days after completing the study due to suicide. Researchers noted that this person had a history of depression and was being treated for attention deficit hyperactivity disorder (ADHD) and sleeping problems prior to entering the study.

**Abnormal blood test results**

Severe or more intense side effects were more common (21%) among participants who had 24 weeks of therapy compared to participants who had 12 weeks of therapy (12%).

In analysing the reports of severe or worse side effects, researchers found that this problem seemed to be driven by the use of atazanavir. This drug is known to cause elevated levels of the waste product bilirubin, the side effect most commonly reported as severe or worse. Furthermore, only one case of elevated bilirubin occurred in a participant who was not taking atazanavir.

Less-than-normal levels of red blood cells occurred in many participants. This was due to the use of ribavirin. However, only in 19% of participants did doctors feel the need to reduce their dose of ribavirin.

Two participants taking ART had their HIV viral loads rise above the 50-copy/ml mark. But in both cases participants disclosed to their doctors that they were not taking their ART exactly as directed.

Among adherent participants, there was a temporary decrease in CD4+ counts of about 100 cells. This occurred because ribavirin temporarily weakens the bone marrow.

**For the future**

Gilead is planning trials of sofosbuvir and the potent anti-HCV agent ledipasvir in co-infected people.

**REFERENCE:**


G. Sofosbuvir + ledipasvir – just six weeks of therapy

As mentioned earlier in this issue of *TreatmentUpdate*, the duration of HCV therapy is shrinking, from 48 weeks a few years ago to 24 weeks and most recently 12 weeks. These shorter periods of therapy are made possible by the use of increasingly powerful anti-HCV drugs called DAAs (direct acting antivirals).

In a trial called Synergy, researchers at the U.S. National Institutes of Health (NIH) tested different combinations of anti-HCV drugs; with the exception of sofosbuvir, all were experimental agents. The drugs used were as follows:

- sofosbuvir (a nucleotide inhibitor of the HCV protein NS5B) – 400 mg once daily
- ledipasvir (an NS5A inhibitor) – 90 mg once daily
- GS-9669 (a non-nuke that inhibits NS5B) – 500 mg once daily
- GS-9451 (a protease inhibitor that inhibits NS3/4) – 80 mg once daily

Here is a list of the regimens used in the study along with the duration of therapy:

- sofosbuvir + ledipasvir – 12 weeks of treatment
- GS-9669 + sofosbuvir + ledipasvir – six weeks of treatment
- GS-9451 + sofosbuvir + ledipasvir – six weeks of treatment

None of the participants had previously been exposed to HCV treatment prior to the current study.

Participants’ average profile at the time they entered the study was as follows:

- 75% men, 25% women
- age – 56 years
- 80–90% of participants were black
- 55–85% had HCV genotype (GT) 1a
• 65–75% of participants had an HCV viral load greater than 800,000 copies
• 75–95% had genes that suggested an unfavourable response to interferon treatment
• 25–40% had severe or extensive liver injury

Researchers noted that this patient population is reflective of what many doctors consider difficult to treat HCV in the U.S.

Results
The response to therapy was stunning given that many participants had factors that would impair their recovery from therapy had they been treated with interferon, and neither interferon nor ribavirin were used in this study. SVR_{12} (an undetectable viral load 12 weeks after a course of therapy has ended) is a very strong predictor of SVR_{24} and highly suggestive of recovery from HCV. SVR_{12} was observed in the following proportions of participants:

• sofosbuvir + ledipasvir – 100% (20 out of 20 participants)
• sofosbuvir + ledipasvir + GS-9699 – 95% (19 out of 20 participants; with one case of relapse)
• sofosbuvir + ledipasvir + GS-9451 – 100% (20 out of 20 participants)

The combination that drove HCV viral load down the fastest was the following:

• sofosbuvir + ledipasvir + GS-9451

By the 14th day of therapy, at least 90% of participants had their HCV viral loads suppressed.

Results – Side effects
According to the researchers, the regimens were well tolerated. No one died during the study.

Common side effects reported were as follows:

• headache – 25%
• fatigue – between 10% and 20%
• diarrhea – between 5% and 25%

Two serious adverse events were reported as follows:

• pain – this occurred in a participant who was recovering from a liver biopsy

REFERENCE:
H. Triple therapy with asunaprevir + daclatasvir + BMS-791325

Bristol-Myers Squibb (BMS) is developing at least the following three anti-HCV agents:

**Daclatasvir**
- impairs the activity of an HCV protein called NS5A
- active against several strains of HCV in lab experiments
- taken at a dose of 60 mg once daily
- has a low potential for drug interactions
- tested in nearly 6,000 participants and appears to be well tolerated

**Asunaprevir**
- impairs the activity of an HCV protein called NS3
- active against several strains of HCV such as genotypes 1, 4, 5 and 6 in lab experiments
- taken at a dose of 100 mg twice daily
- studied in more than 2,000 participants

**BMS-791325 (’325)**
- impairs the activity of NS5B
- is a polymerase inhibitor
- active against several strains of HCV including genotypes 1, 3, 4, 5 and 6 in lab experiments
- taken twice daily at a dose of 75 mg or 150 mg
- studied in more than 500 participants

For the study reported here, researchers gave participants 12 consecutive weeks of therapy.

- daclatasvir was given at a dose of 30 mg twice daily
- asunaprevir was given at a dose of 200 mg twice daily

BMS plans to put these drugs into a single pill in the future.

The average profile of participants at the start of the study was as follows:

- 67% men, 33% women
- age – 54 years
- 82% of participants had HCV genotype 1a and 18% had genotype 1b
- HCV viral load – 2.5 million IU/ml
- 9% of participants had severe liver injury (cirrhosis) confirmed by biopsy
- 46% of participants had no or minimal liver injury

Researchers gave all participants daclatasvir and asunaprevir in the dose and schedule previously mentioned, and then randomly assigned them to receive one of the following two doses of BMS ’325:

- 75 mg twice daily – 80 participants
- 150 mg twice daily – 86 participants

**Results – SVR$_{12}$**

According to the interim analysis, the rates of SVR$_{12}$ (highly suggestive of cure) were distributed as follows:

- 3 DAAs (including ’325 given at a dose of 75 mg twice daily) – 88.8%
- 3 DAAs (including ’325 given at a dose of 150 mg twice daily) – 89.5%

Data are incomplete for five missing participants and researchers are attempting to locate these people.

Among those without an SVR$_{12}$ (11 participants) there were five breakthroughs by HCV and six others relapsed.

Five participants had mutations that conferred resistance to asunaprevir and daclatasvir and six participants had HCV that had become resistant to all three drugs.

Eight participants prematurely left the study for the following reasons:

- throat tumour – one person
- throat tightness – one person
- lack of effectiveness – three people
- abdominal infection – one person
- imprisonment – two people

According to researchers, ’325 was well tolerated.

Common side effects reported in this study were as follows:

- headache – 25%
- diarrhea – 15%
- fatigue – 11%
- nausea – 10%
Abnormal blood test results

- one case of the elevated liver enzyme AST on day 24 of the study; this returned to normal 50 days after the study began
- two cases of elevated blood sugar; both occurred in participants with a history of type 2 diabetes

Bear in mind

The present study and its results should be considered preliminary in nature. Still, they showcase a trio of drugs that are relatively powerful, with cure rates approaching 90%. This happened in a regimen free of interferon and ribavirin among participants with the difficult-to-treat strain of HCV—genotype 1a.

Further studies with this combination of BMS drugs are underway. These studies have the code name Unity One (which will enroll participants without cirrhosis who have not been previously treated) and Unity Two (which will have participants with cirrhosis).

In case of resistance

When one of the study physicians was asked about possible salvage regimens for participants who developed resistance to the study medicines, he suggested that the following strategies be considered:

- sofosbuvir + ribavirin
- sofosbuvir + interferon + ribavirin
- wait until the drug-resistant HCV has disappeared from their blood

REFERENCE:

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.

CATIE (Canadian AIDS Treatment Information Exchange) in good faith provides information resources to help people living with HIV/AIDS and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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What CATIE Does

CATIE is Canada’s source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life.

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. CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

CATIE Publications

TreatmentUpdate
CATIE’s flagship treatment digest on cutting-edge developments in HIV/AIDS and hepatitis C research and treatment. Subscribe to TreatmentUpdate and automatically receive an email notifying you the moment a new issue is available online or contact us at 1.800.263.1638 to receive a print subscription.

CATIE News
CATIE’s bite-sized HIV and hepatitis C news bulletins.

HepCInfo Updates
CATIE’s bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

A Practical Guide to HIV Drug Treatment
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects
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.

The Positive Side magazine
Holistic health information and views written by and for people living with HIV.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

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