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I ANTI-HIV AGENTS

A. The emergence of dual drug therapy

Potent combination anti-HIV therapy (ART) became available in 1996 in Canada and other high-income countries. The arrival of ART marked an important turning point in the history of the HIV pandemic: for the first time, treatment was able to durably suppress HIV levels in the blood, allowing the immune system to partially rebuild itself. As a result, many ART users experienced sustained recovery from life-threatening infections, inexorable weight loss and AIDS-related cancers. These effects of ART are so profound that researchers expect that many ART users will have near-normal life expectancy.

Grappling with complexity

In 1996 and for many years after, initial ART regimens were complex, consisting of multiple pills taken two or three times daily, oftentimes with food restrictions. Furthermore, these early regimens had unpleasant, sometimes distressing side effects.

The combinations of ART that became the mainstay in 1996 and thereafter set the standard for what was considered an acceptable treatment regimen: a combination of three or four drugs. Each regimen was anchored by a powerful drug such as a protease inhibitor or a non-nuke (non-nucleoside reverse transcriptase inhibitor; NNRTI). In first-line therapy today, the anchor drug in a regimen is usually an integrase inhibitor. Integrase inhibitors are powerful, generally well tolerated, and tend to have fewer drug interactions than other anchor drugs.

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A move toward simplification

Some pharmaceutical companies are beginning to challenge the concept of triple- or quadruple-drug regimens for HIV. For instance, Viiv and Janssen have collaborated on a treatment that pairs the integrase inhibitor dolutegravir (Tivicay and found in Triumeq) with the non-nuke rilpivirine (Edurant and in Complera) in a pill called Juluca.

Juluca is meant to be used as part of induction-maintenance strategies. That is, doctors first prescribe a more complex three- or four-drug regimen (induction phase) to suppress a person's viral load. Once this happens and the person's viral load continues to be suppressed, the regimen can be changed to Juluca (maintenance phase).

The use of induction-maintenance treatment is also being explored in phase III clinical trials with long-acting formulations of two drugs: the experimental integrase inhibitor cabotegravir and the non-nuke rilpivirine. These drugs are injected into the buttocks, where they are slowly released into circulation. Prior to starting the injectable formulations, patients are first started on oral formulations of triple therapy that includes rilpivirine and cabotegravir. The oral formulations are taken for about six months to ensure that there are no problems tolerating these drugs when the injectable formulations are used later on.

There are rumours that a powerful and long-acting experimental nucleoside analogue code-named MK-8591, made by the pharmaceutical company Merck, may be paired with another HIV medication for yet another dual-drug option for HIV treatment in the future.

Back to initial treatment

Although the examples provided above are about induction-maintenance, one pair of drugs is being tested for the initial treatment of HIV: dolutegravir + 3TC (lamivudine). Dolutegravir is a powerful integrase inhibitor and 3TC is a nuke that has a good track record of safety over the past 25 years. In clinical trials, initial treatment with the combination of dolutegravir + 3TC has similar effectiveness to a combination of dolutegravir + Truvada (tenofovir DF + FTC).

As several dual-drug regimens are being developed, their eventual licensure is likely to have an impact

on HIV treatment guidelines in high-income countries. When helping patients choose a regimen, doctors have to balance many factors, including at least the following:

- the presence/absence of HIV that has partial or full resistance to a drug or class of drugs
- tolerability
- the ability to take pills every day
- interactions with medicines used to treat other common conditions (such as high blood pressure, type 2 diabetes, abnormal cholesterol levels, depression, sleeping problems, etc.). In general, integrase inhibitors tend to have the fewest interactions with other drugs.

HIV is a chronic infection that is kept under control with ART. Will dual-drug regimens provide long-lasting control? So far, clinical trials of dual drug regimens that have been tested for two years (such as Juluca) suggest that is the case. Two-year results from trials of dolutegravir + 3TC are eagerly awaited.

If the two-year data for dolutegravir + 3TC as initial HIV therapy are robust, doctors and patients will have to reckon with another challenge to the received wisdom accumulated since 1996—that dual-drug regimens may be, in some circumstances, as good as standard triple or quadruple therapy for the initial treatment of HIV. Changing accepted practices in medicine is not easy. Many patients and their doctors feel comfortable and safe with triple-drug therapy. Thus, the use of dual regimens will likely happen slowly over time. As more data from clinical trials accumulate, doctors and their patients may gain more confidence about the use of dual drug therapy for HIV.

B. Dolutegravir + 3TC for the initial treatment of HIV

As mentioned earlier in this issue of *TreatmentUpdate*, researchers are testing simplified regimens for maintenance treatment for HIV. Results from pilot studies of dual drug regimens have suggested that dolutegravir (Tivicay) and 3TC (lamivudine) can help about 90% of people who *initiate* treatment with this combination to achieve a viral load less than 50 copies/mL.

To explore the potential of dolutegravir + 3TC as initial dual drug therapy, researchers conducted two randomized, placebo-controlled clinical trials called Gemini 1 and Gemini 2, comparing the following regimens for initial treatment:

- dolutegravir + 3TC
- dolutegravir + Truvada (tenofovir DF + FTC)

At the 48th week of the study, similar proportions of participants on both regimens had a viral load less than 50 copies/mL:

- dolutegravir + 3TC – 90%
- dolutegravir + Truvada – 93%

Further details appear later in this report. The 96-week trial results from Gemini 1 and 2 are awaited. Should the results be similar to those seen in week 48, it is likely that a single pill containing dolutegravir + 3TC for the initial treatment of HIV infection will be approved in the U.S. in the spring of 2019 and in Canada in mid-summer 2019.

Study details

Participants for Gemini 1 and 2 were recruited from North and South America, Europe, South Africa, South Korea and Taiwan. The data from the two trials were pooled for analysis, as the trials were identical in design.

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

- age – 32 years; about 10% of participants were 50 years or older
- 85% males, 15% females
- major ethno-racial groups: white – 68%; black – 13%; Asian – 10%
- HIV viral load – 28,000 copies/mL (Note that 20% of participants had a viral load of 100,000 copies/mL. Furthermore, about 4% of participants had a viral load greater than 500,000 copies/mL.)
- CD4+ count – 430 cells/mm³
- no participants had hepatitis B or C virus co-infection
- no participants had HIV that was resistant to the study drugs

A total of 716 people received dolutegravir + 3TC and 717 people received dolutegravir + Truvada.

Results—Focus on viral loads and CD4+ cell counts

At the 48th week of the study, the results were as follows:

The proportions of participants with a viral load less than 50 copies/mL (undetectable) were distributed as follows:

- dolutegravir + 3TC – 91%
- dolutegravir + Truvada – 93%

This difference was not statistically significant and shows that the regimen of dolutegravir + 3TC is similarly effective to a standard three-drug regimen of dolutegravir + Truvada.

Among other participants, no virological data was available at week 48 for the following proportions of participants:

- dolutegravir + 3TC – 6%
- dolutegravir + Truvada – 5%

Finally, the proportions of participants who were unable to achieve an undetectable viral load at week 48 were distributed as follows:

- dolutegravir + 3TC – 3%
- dolutegravir + Truvada – 2%

High vs. low viral loads

There was no significant difference in the proportions of participants able to achieve a suppressed viral load at week 48 when analysed by their viral load levels at the start of the study. However, among participants who entered the study with a low CD4+ count (200 or fewer cells/mm³), there appeared to be a difference in the proportions who achieved an undetectable viral load, as follows:

- dolutegravir + 3TC – 79% (50 out of 63 people)
- dolutegravir + Truvada – 93% (51 out of 55 people)

The overall number of participants with a CD4+ count of 200 or less was relatively small, so statistically robust conclusions cannot be drawn from this difference in outcome. However, it is possible, likely even, that people with 200 or fewer

cells/mm³ who start a dual drug regimen will not do as well as people with that cell count who start a standard triple-drug regimen.

There were relatively few people who developed virological failure (less than 1% of participants), distributed as follows:

- dolutegravir + 3TC – 6 people (less than 1%)
- dolutegravir + Truvada – 4 people (less than 1%)

Among these people, there were no cases of HIV resistant to the classes of drugs used in this study—nucleoside analogues and integrase inhibitors.

Changes in CD4+ cell counts

Participants' average CD4+ cell counts rose by about 220 cells/mm³ regardless of the study regimen used. That is, their average CD4+ count rose from 430 cells/mm³ at the start of the study to 650 cells/mm³ about a year later.

Focus on complications and side effects

The term *adverse events* is used by researchers to describe a range of unfortunate events that can occur to people in a clinical trial. Those events may be caused by drug side effects, the underlying disease process or circumstances outside of the clinical trial.

In the analysis of Gemini 1 and 2, adverse events judged by investigators to be related to the study drugs were distributed as follows:

- dolutegravir + 3TC – 18% (126 people)
- dolutegravir + Truvada – 24% (169 people)

Most of these drug-related adverse events were graded as mild and included the following issues:

- headache
- diarrhea
- nausea

Side effects that were of at least moderate intensity, such as headache, were distributed as follows:

- dolutegravir + 3TC – 6%
- dolutegravir + Truvada – 7%

Adverse events leading to premature departure from the study were distributed as follows:

- dolutegravir + 3TC – 2%
- dolutegravir + Truvada – 2%

There was no clear pattern of side effects leading to premature withdrawal from the study.

Focus on the brain

Previous randomized studies with dolutegravir found that a relatively small proportion of participants developed brain-related side effects that likely led them to leave the study prematurely. These side effects include problems with sleep, mood (anxiety and depression) and concentration. The distribution of brain-related side effects that caused people to prematurely leave the study were as follows:

- dolutegravir + 3TC – 6 people (less than 1%)
- dolutegravir + Truvada – 4 people (less than 1%)

There was no clear pattern to the distribution of brain-related side effects that caused some people to leave the Gemini studies prematurely. The distribution was as follows:

Depression

- dolutegravir + 3TC – 1 person
- dolutegravir + Truvada – 1 person

Sleeping problems

- dolutegravir + 3TC – 2 people
- dolutegravir + Truvada – 0 people

Thoughts of self-harm

- dolutegravir + 3TC – 1 person
- dolutegravir + Truvada – 1 person

Attempted suicide

- dolutegravir + 3TC – 1 person
- dolutegravir + Truvada – 1 person

Psychotic disorder

- dolutegravir + 3TC – 1 person
- dolutegravir + Truvada – 0 people

Psychosis due to harmful intake of alcohol

- dolutegravir + 3TC – 0 people
- dolutegravir + Truvada – 1 person

Street drug overdose

- dolutegravir + 3TC – 0 people
- dolutegravir + Truvada – 1 person

Looking at kidney and bone health

Truvada contains tenofovir DF, the older formulation of tenofovir. In a minority of people, use of tenofovir DF is associated with an increased risk of kidney injury. In the data from Gemini 1 and 2, serious kidney injury or serious kidney dysfunction was not common. However, assessments of blood and urine samples suggested better overall kidney health among people who used dolutegravir + 3TC vs. dolutegravir + Truvada.

A similar trend was seen for proteins in the blood associated with bone health. That is, participants who used dolutegravir + 3TC were less likely than participants who used dolutegravir + Truvada to have proteins associated with reduced bone density. However, these findings are not definitive and a subset of participants should have undergone low-dose X-ray scans (DEXA) of their bones to give a clear analysis of the effects of the study drugs on bone health.

Two people died in the Gemini study—one from a heart attack and the other from complications related to cancer (lymphoma). Both participants were taking dolutegravir + 3TC and were enrolled in Gemini 2. However, investigators considered their deaths unrelated to the study drugs.

Bear in mind

The combination of dolutegravir + 3TC is more or less as effective as standard triple therapy (dolutegravir + Truvada) for the treatment of initial HIV infection in people who have more than 200 CD4+ cells/mm³. Overall, there were fewer side effects with dolutegravir + 3TC than with dolutegravir + Truvada.

Gemini 1 and 2 are ongoing studies that will continue for about three years.

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C. Dual maintenance therapy with dolutegravir + rilpivirine

A pill containing two anti-HIV drugs—dolutegravir + rilpivirine—has been approved for use in Canada, the European Union and the United States. This pill is sold under the brand name Juluca and is meant to be used as maintenance treatment. With maintenance treatment, a patient first has their HIV viral load suppressed with a standard combination of three- or four-drug regimens (this is sometimes called induction therapy). Once their viral load has been suppressed (less than 50 copies/mL) and stays suppressed, their doctor may offer to replace their current regimen with a simplified regimen of the two drugs in Juluca.

In clinical trials called Sword 1 and Sword 2, researchers tested a combination of dolutegravir + rilpivirine in more than 1,000 participants for up to two years. At the end of this time, 89% of participants taking Juluca had a viral load less than 50 copies/mL, attesting to the combination's power and tolerability.

The 48-week results from Sword 1 and Sword 2 were previously reported here:

<https://www.catie.ca/en/treatmentupdate/treatmentupdate-224/anti-hiv-agents/dolutegravir-rilpivirine-maintenance-therapy>

In this issue of *TreatmentUpdate*, we largely focus on results after week 52.

The data from Sword 1 and Sword 2 were pooled for the present analysis, as the two trials were identical in design.

Participants who had been taking potent combination anti-HIV therapy (ART) and had a viral load less than 50 copies/mL on standard three- or four-drug regimens were randomly assigned to receive one of the following interventions:

- Juluca, one pill taken once daily with food – 513 people
- continue their current anti-HIV regimen (CAR) for the first 52 weeks of the study, then switch to Juluca – 511 people

Additionally, after 52 weeks in the study, participants who were still on standard ART had their regimens switched to Juluca. Thus, from week 52, everyone in the study was taking Juluca. All participants will be monitored for a total of 144 weeks, but the current analysis provided data for the first 100 weeks of the study.

The average profile of participants upon entering Sword 1 or Sword 2 was as follows:

- age – 43 years
- 22% females, 78% males
- major ethno-racial groups: white – 80%; black – 8%; Asian – 9%; Indigenous – 3%
- CD4+ count – 600 cells/mm³
- viral load – less than 50 copies/mL

Commonly used regimens before participants were randomized to the study regimens included the following:

- Atripla (efavirenz + tenofovir DF + FTC)
- raltegravir (Isentress) + Truvada (tenofovir DF + FTC)
- darunavir (Prezista) + ritonavir + Truvada

Results

As participants entered the study with undetectable viral loads (less than 50 copies/mL), researchers were interested in the proportions of participants who maintained this suppression:

Week 48

- Juluca – 95%
- CAR – 95%

Week 100

- Juluca taken week 1 to 100 – 89%
- Juluca taken week 52 to 100 – 93%

These differences in the proportions of participants with a suppressed viral load were not statistically significant. Thus, Juluca is considered similarly effective as maintenance treatment compared to standard triple therapy.

The proportions of participants whose regimens were never able to get below the 50-copies/mL mark (this was considered “virological failure” by the researchers) were as follows:

- Juluca taken week 1 to 100 – 13 people (3%)
- Juluca taken week 52 to 100 – 10 people (2%)

Analysis of stored blood samples suggested that in some cases where virological failure occurred, participants had entered the study with HIV that had partial resistance to dolutegravir or rilpivirine.

Some participants’ data were not available for the analysis at the 100-week mark because they had left the study for a variety of reasons, such as treatment failure, personal choice, side effects, change in residence, pregnancy, and so on.

Complications and side effects

The term *adverse events* is used by researchers to describe a range of unfortunate events that can occur to people in a clinical trial. Those events may be caused by drug side effects, the underlying disease process or circumstances outside of the clinical trial.

Common general side effects in participants taking Juluca were nausea (2%) and headache (2%). These were generally mild and temporary.

The proportions of participants who left the study because of bothersome side effects were as follows:

- Juluca taken week 1 to 100 – 7%
- Juluca taken week 52 to 100 – 3%

Focus on the brain

The drugs inside Juluca—dolutegravir + rilpivirine—can enter the brain. This is good because there are HIV-infected cells in the brain. However, a downside is that these drugs can sometimes have side effects that can affect a person’s mood and sleep. The proportions of participants who left the study prematurely because of brain-related side effects were distributed as follows:

- Juluca taken week 1 to 100 – 34 people (7%)
- Juluca taken week 52 to 100 – 15 people (3%)

Specific brain-related adverse effects that led to some participants leaving the study prematurely were distributed as follows:

Juluca taken week 1 to 100

- anxiety – 4 people
- related to depression – 4 people
- thoughts of self-harm – 4 people
- sleeping problems – 2 people
- nightmares – 1 person
- committed suicide – 1 person

Juluca taken week 52 to 100

- sleeping problems – 3 people
- related to depression – 3 people
- confusion – 1 person
- loss of libido – 1 person
- “diminished motivation” – 1 person
- thoughts of suicide – 1 person

Due to the study design, it is not clear what proportion of neuropsychiatric events were caused by exposure to Juluca between week 52 and 100. However, a look at the 48-week results from the trial may be useful in assessing the distribution of mental health side effects:

<https://www.catie.ca/en/treatmentupdate/treatmentupdate-224/anti-hiv-agents/dolutegravir-rilpivirine-maintenance-therapy>

Analysis of blood and urine tests

Bones

Low-dose X-ray scans (called DEXA) are the gold standard for assessing bone mineral density. However, in the present studies, rather than using DEXA, researchers assessed levels of certain proteins in the blood that are associated with changes in bone density. They found that, overall, Juluca likely had a neutral effect on bones.

Kidneys

Blood and urine tests suggested a modest improvement in kidney health over the course of the study.

Lipids—cholesterol and triglycerides

Juluca did not appear to have a significant impact on changes in lipid levels in the blood.

For the future

The results from Sword 1 and Sword 2 are promising. They suggest that maintenance therapy with Juluca is possible and can be successful in many patients. Clinical trials with Juluca will continue until week 144.

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D. Italian study explores dual drug regimens as maintenance treatment

The drug dolutegravir is a widely used part of combination therapy for HIV treatment. Dolutegravir belongs to a class of drugs called integrase inhibitors; it is powerful and generally well tolerated. Dolutegravir is sold under the following brand names and fixed-dose combinations:

- Tivicay – dolutegravir
- Juluca – dolutegravir + rilpivirine
- Triumeq – dolutegravir + 3TC + abacavir

Investigating dolutegravir-containing combinations

A pill containing two drugs—dolutegravir + 3TC—is currently in clinical trials for the initial treatment of HIV infection. Results from the first year of those trials suggest that the combination is very promising. It is likely that the combination of dolutegravir + 3TC will be approved by regulatory agencies in Canada and other high-income countries sometime in 2019.

A recent study from Alberta (<https://www.catie.ca/en/catieneews/2018-08-23/alberta-clinic-explores-long-term-survival-among-hiv-positive-people>) found that over the course of 20 years some long-term survivors have been taking kilograms of medicines. In light of that, maintenance or even initial therapy with just two drugs (instead of the standard three- or four-drug combinations) can reduce the burden of medicines and potentially result in fewer side effects and/or drug interactions.

Comparing dual drug regimens

Researchers at several clinics in Italy have conducted an observational study of induction-maintenance therapy for HIV. In the induction phase of this approach to treatment, patients are given standard three- and four-drug combinations. Once their viral load has been suppressed to 50 copies/mL and stays suppressed for some time afterward (usually a period of months), doctors can offer maintenance therapy by reducing their regimen to just two drugs.

In the Italian study, researchers analysed data from 419 people who had stable and suppressed viral loads on standard regimens and who were later switched to one of the following dual drug combinations:

- dolutegravir + 3TC – 229 participants
- dolutegravir + rilpivirine – 187 participants

Participants were monitored for about two years while they were on these simplified regimens.

The researchers found that around 90% of participants maintained a suppressed viral load over the course of the study. Both dual drug regimens were associated with improvements in cholesterol levels in the blood and were generally well tolerated.

An important additional finding from the Italian study was that participants who several years prior to the present clinical trial had a viral load greater than 500,000 copies/mL were at increased risk for experiencing virological failure during the present study.

Study details

The present study was retrospective in design. That is, researchers analysed data that had been collected previously for another purpose—to compare dual drug regimens. Participants were not randomly assigned to the study regimens.

The researchers defined virological failure in one of the following ways:

- having two consecutive viral load test results of 50 copies/mL or greater over a period of three months
- having a single viral load test result that was 1,000 copies/mL or greater

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

- age – 53 years
- 72% men, 28% women
- 21% of participants had been exposed to hepatitis C virus (HCV)
- 44% had one of their pre-study regimens fail
- length of time since HIV diagnosis – 16 years
- viral load – less than 50 copies/mL
- CD4+ count – 670 cells/mm³

Results

The overall proportions of participants whose viral load was suppressed and stayed suppressed two years after entering the study were distributed as follows:

- dolutegravir + 3TC – 95%
- dolutegravir + rilpivirine – 97%

So, overall, the regimens have similar effects.

However, researchers noticed one difference in the proportions of people who achieved viral suppression, and this was related to their historical viral load. That is, researchers found that participants whose highest-ever viral load prior to entering the study was 500,000 copies/mL or greater were at heightened risk for developing virological failure in the present study, regardless of which dual drug combination they took.

Among participants taking dolutegravir + 3TC who had a viral load of 500,000 copies/mL or greater at some point before entering the present study, the proportions who achieved a suppressed viral load during the study were as follows:

- week 48 – 95%
- week 96 – 87%

Among participants taking dolutegravir + rilpivirine who had a viral load of 500,000 copies/mL or greater at some point before entering the present study, the proportions who achieved a suppressed viral load during the study were as follows:

- week 48 – 92%
- week 96 – 88%

Adverse events

The term *adverse events* describes a range of unfortunate events that can occur in a clinical trial. These events may be due to drug side effects, the underlying disease process or issues outside of the clinical trial.

Dolutegravir + 3TC

A total of 30 participants (13%) left the study prematurely. The main reasons for their departure were as follows:

- neuropsychiatric events (including sleeping problems, anxiety, depression) – 8 people
- virological failure – 6 people
- wanting to take a single-tablet regimen – 4 people
- gastrointestinal problems – 1 person
- hypersensitivity reaction – 1 person

Dolutegravir + rilpivirine

A total of 13 participants (7%) left the study prematurely. The main reasons for their departure were as follows:

- neuropsychiatric events (including sleeping problems, anxiety, depression) – 3 people
- virological failure – 2 people
- gastrointestinal problems – 2 people
- kidney injury – 1 person

Changes to lab test results

On average, levels of total cholesterol fell after participants began taking dual drug regimens.

No significant changes in tests of kidney health occurred during the course of the study.

Bear in mind

The present study is retrospective in nature. It used data collected for one purpose in the past, then analysed that data for the purposes of this study. Conclusions drawn from retrospective studies must be taken cautiously, as such studies are not the most statistically robust. Despite this caveat, the findings from the Italian study are broadly similar to results from randomized clinical trials of dual drug regimens containing dolutegravir.

The overall range of neuropsychiatric side effects in the present study was about 4%. This is within the range reported from other studies.

The association between previously having a high viral load (500,000 copies/mL and greater) and an increased risk of virological failure while subsequently on dual drug therapy is interesting. It may serve as a cautionary note about the limits of dual therapy.

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E. Dual drug therapy—impact on the HIV reservoir

As explained earlier in this issue of *TreatmentUpdate*, clinical trials with dual drug regimens based on the powerful integrase inhibitor dolutegravir are underway. One dual drug combination, Juluca (dolutegravir + rilpivirine), has already been approved for use in Canada and other high-income countries. Juluca is meant for use as simplification in place of more complex regimens among patients whose viral loads are less than 50 copies/mL and have been that way for some time. Another combination, dolutegravir + 3TC, is expected to be approved in 2019 in Canada and other high-income countries.

About the reservoir

After HIV infection has occurred, the virus becomes established in cells of the immune system—T-cells and a group of relatively long-lived cells called monocytes (in their mature form these are called macrophages). Monocytes/macrophages travel throughout the body, spending time in major organ-systems. As a result, HIV-infected cells are found in many parts of the body, including the following:

- brain and spinal cord
- the immune system: lymph nodes and lymphoid tissues as well as organs such as the spleen, bone marrow and thymus gland
- lungs

- kidneys
- fatty tissues

Although potent combination anti-HIV therapy (ART) greatly suppresses the production of HIV in the blood, some studies suggest that small amounts of HIV are still produced in lymph nodes.

Researchers refer to the burden of HIV-infected cells in the body as the reservoir. Studies are underway to try to reduce and possibly eliminate this burden.

An important question about dual drug therapy is its impact on the reservoir.

The Verona study

Researchers at the University of Verona in Italy conducted a pilot study to assess the impact of induction-maintenance therapy. All participants who were new to ART were initially treated with standard triple-drug therapy, in this case Triumeq (dolutegravir + 3TC + abacavir). After participants had achieved and maintained viral suppression for 12 consecutive months, their regimens were simplified to dolutegravir + 3TC.

In 14 participants who were able to undergo dual therapy for between one and eight months, researchers found no significant differences in the burden of infected cells in their blood samples compared to the level of these cells after 12 months of taking triple therapy.

Thus, data from this pilot study strongly suggest that induction-maintenance therapy does not increase the size of the HIV reservoir, at least over the short term. Longer and larger studies should be done to confirm this finding.

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F. Combinations of super antibodies may keep HIV at bay

Although effective HIV treatment (ART) exists, researchers are studying other potential treatments such as a group of antibodies that are highly efficient at binding to and neutralizing HIV. Scientists call these super antibodies “broadly neutralizing antibodies” (bNAbs). After these antibodies bind to HIV and HIV-infected cells, they then engage the immune system to help destroy HIV and infected cells. While anti-HIV pills have to be taken every day, it is possible that bNAbs, which are given by intravenous infusion, are an approach to HIV treatment that, if found effective, could be given less frequently, perhaps every three weeks or even with longer intervals.

Researchers have tested bNAbs as single agents (that is, giving one type of antibody at a time), but HIV can quickly develop the ability to resist one antibody when used in this way. Just as effective HIV treatment requires a combination of drugs, it is very likely that effective antibody therapy will require combinations of bNAbs.

Researchers in the U.S. have tested a combination of two antibodies in 15 participants who had been taking ART for many years and who had very low viral loads. Participants received the infusions of antibodies at weeks 0, 3 and 6 of the study; ART was discontinued two days after the first infusion. Nine of the 15 participants were able to maintain an undetectable viral load while off ART for an average of four months after the final infusion of antibodies. None of these nine developed HIV that was resistant to the antibodies. The results from this pilot study are exciting and raise many issues that need to be taken into account for future studies of bNAbs.

Study details

Researchers recruited participants who had been taking ART for at least 24 months and who had viral loads in their blood less than 50 copies/mL for at least 18 months. Furthermore, in assessments done prior to entry in the study participants were expected to have a viral load of less than 20 copies/mL using a more sensitive viral load assay and their CD4+ counts were expected to be greater than 500 cells/mm³.

All participants had blood drawn for an assessment that checked if their HIV was sensitive or susceptible to the antibodies used in the study.

Participants received three intravenous infusions of antibodies given at a dose of 30 mg per kilogram of body weight at weeks 0, 3 and 6 of the study.

Participants underwent frequent assessments during the study, with blood being drawn every one to two weeks. If their viral load was found to be more than 200 copies/mL, then they would restart ART.

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

- 14 men, 1 woman
- age – 40 years
- major ethno-racial groups: white – 40%; black – 27%; Hispanic – 27%
- length of time since HIV diagnosis – 6 years
- CD4+ count – 730 cells/mm³
- viral load – less than 20 copies/mL

Note that only 11 out of the 15 participants had HIV that was sensitive or susceptible to the antibodies used in the study. These 11 participants became the focus of research.

The antibodies used had the following code names:

- 3BNC117
- 10-1074

Results

Nine out of the 11 participants were able to maintain an undetectable viral load while off ART for an average of four months after the final infusion of antibodies.

The antibodies had no significant impact on the reservoir of HIV-infected cells in the body.

Bear in mind

The present study is very encouraging. It shows that a combination of two antibodies has the potential to keep HIV suppressed in certain people who have interrupted ART—those who have low pre-study viral loads (less than 20 copies/mL) and who have HIV that is sensitive to the antibodies.

Many exciting scientific questions arising from the present study need to be explored in future clinical trials:

- What is the ideal number of bNAbs to use: Is it two, three or four antibodies?
- More than 10 bNAbs have been discovered. Which ones should be used in studies?
- How often should antibody infusions be given and how much?
- Should bNAbs be used with other drugs that can enhance the functioning of the immune system, such as vesatolimod (GS-9620; discussed later in this issue of *TreatmentUpdate*) and a class of drugs called checkpoint inhibitors (currently used to treat some cancers)?

It will take years to get answers to these questions, so much research lies ahead.

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G. Monkey study uncovers the potential for vesatolimod and antibodies in cure research

The immune system has many different mechanisms for detecting bacteria, fungi and viruses. One such mechanism uses a series of proteins called toll-like receptors (TLR). One of these proteins, called TLR-7, has been the focus of much research. After it senses the genetic material of a virus, TLR-7 helps to activate certain cells of the immune system to respond with the production of antiviral substances.

Vesatolimod (also known under the code name GS-9620) is an experimental drug that interacts with TLR-7. The reason for testing vesatolimod is that researchers hope that by interacting with TLR-7 it can help increase the immune system's ability to sense and attack HIV and HIV-infected cells.

Vesatolimod has previously been tested at relatively low doses in people with chronic hepatitis B virus (HBV) infection. The drug was safe but did not significantly increase cure rates of HBV when used at doses between 1 and 4 mg taken once weekly for 12 consecutive weeks.

From SIV to HIV to SHIV

In susceptible monkeys, simian immunodeficiency virus (SIV) causes an AIDS-like condition. This virus is closely related but not identical to HIV. It is likely that some form of SIV was the ancestor of HIV. However, because there are differences between SIV and HIV, it means that monkeys infected with SIV do not always respond well to drugs designed to treat HIV (ART) or vaccines designed to protect against HIV. Testing ART and vaccines in monkeys is an important step before further testing in humans. To gain a fuller understanding of the response of the monkey immune system to ART and vaccines, researchers have created a hybrid virus using elements of both SIV and HIV. Scientists call the resulting hybrid virus "SHIV" and it has been used for more than 20 years in laboratory experiments with monkeys.

An important monkey experiment

Researchers in the U.S. have conducted experiments with monkeys infected with SHIV. Shortly after infection they gave the monkeys ART. Subsequently, some monkeys received no additional intervention, some received vesatolimod, some received the broadly neutralizing antibody (bNAb) PGT121, and still other monkeys received both vesatolimod and PGT121. Researchers then discontinued giving some of the monkeys ART.

Researchers found that the combination of vesatolimod and PGT121 delayed the resurgence of virus that occurs after interruption of ART. Five of the 11 monkeys given both drugs did not have a resurgence of virus for more than six months after researchers withheld ART. Also, researchers found it difficult to detect virus samples from these five monkeys. The combination of vesatolimod and a powerful antibody has the potential to be tested in HIV-positive people, perhaps allowing them to safely interrupt ART and potentially reducing their burden of HIV-infected cells.

Study details

Researchers used 40 monkeys, all of which received ART shortly after infection with SHIV. The monkeys were divided into subgroups and some received additional agents:

- no additional intervention
- vesatolimod
- PGT121
- vesatolimod + PGT121

Doses of experimental drugs

A total of 10 doses of vesatolimod were given orally every two weeks.

Monkeys received five intravenous infusions of the antibody PGT121 every two weeks for about four and a half months.

Eventually the interventions were stopped, the monkeys were monitored and blood samples from all the monkeys were analysed and compared.

Key findings

Monkeys treated with both vesatolimod and PGT121 had significantly lower levels of SHIV-infected cells in their lymph nodes. This suggests that the combination of these two interventions may be able to reduce the burden of virus-infected cells in the bodies of monkeys with SHIV. Also, monkeys who received both interventions showed a significantly increased delay to the resurgence of virus in their blood after cessation of ART.

Monkeys that had the longest delay in resurgent virus tended to have lower levels of SHIV during their initial infection (prior to treatment with ART). This suggests that SHIV probably did not spread as far in the bodies of monkeys with low viral loads prior to initiation of ART.

Bear in mind

The results from the monkey studies are very promising. They suggest that a combination of vesatolimod and PGT121 (or perhaps another powerful antibody) can help keep SHIV in check for about six months after cessation of ART in some SHIV-positive monkeys. Also, the combination of drugs has the potential to reduce the burden of SHIV-infected cells in monkeys.

The results from the study in monkeys raise the following possibility:

The combination of vesatolimod and PGT121 could, in theory, allow for an interruption of ART and increase the chances of a cure for HIV in people who respond to this combination.

However, there are at least three aspects of the present study that are cause for caution when interpreting and extending the results of the monkey study to humans:

- Monkeys were treated with ART soon after they were infected. In contrast, historically, most people begin HIV treatment months or even years after HIV infection was diagnosed.
- Monkeys who had a low viral load prior to initiation of ART appeared to be the ones able to respond best to the combination of vesatolimod and PGT121.
- A hybrid virus, SHIV, was used in the experiments. Some researchers have noted that SHIV “is potentially easier for the monkey immune system to control than other monkey viruses.”

Despite these caveats, the results of the current experiment have encouraged some researchers to begin planning studies in HIV-positive people with vesatolimod and broadly neutralizing antibodies.

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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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