



Welcome to the first issue of **Community Conference Watch**, a user-friendly and easy-to-understand newsletter

that brings you select samples of clinical trial results of recent studies from major HIV science conferences. Our goal is to provide the HIV and hepatitis communities with helpful insights that will assist our readers in understanding the **ins and outs** of clinical trials. Examples of trials contained in this issue are from the **VII International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland.**

Community Conference Watch



Issue 1

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Helpful Tools

Glossary Some words in this newsletter may be new to you. If you see a word that is ***bold italic*** with quotes, look it up in the Glossary in the middle of the newsletter to see what it means.

TRIAL Watch
In this newsletter, we cover different clinical trials that were presented at conferences. Reading about this new information is one thing, but really understanding the ins and outs of the trial is another. Read the "Trial Watch" section for take-home messages, comments about the trial design, and who this information might be particularly important to. To help guide you, we are also using the following symbols to help you find information quickly about the trial:

TE **Treatment experienced** (for those who have taken one or more HIV treatment regimens before)

ST **"Salvage therapy"** (for those that are running out of treatment options, and are waiting for much-needed information on new drugs)

TN **"Treatment naïve"** (for those who have never taken anti-HIV drugs before)

LH **Liver health** (for those who are co-infected with hepatitis (HBV or HCV) or need to pay special attention to their liver because of hepatotoxicity)

D **Durability** (these trials study how long and how well a drug regimen lasts at keeping HIV down)

H2H **Head-to-Head** (these trials compare 2 similar drugs to each other)

To find out if this newsletter is for you, ask yourself these questions:

Q: How do you get the latest news about HIV, hepatitis or any other diseases that you care about? **A:** If, "huh?" or "I don't know" is your answer, this newsletter is for you.

Q: Why is it important to get the latest news? **A:** (1) There is no cure for HIV. (2) **"Hepatitis"** C (HCV) can be cured, but not easily and not in everyone. (3) Hepatitis B (HBV), herpes, and human papilloma virus (HPV) are very complex and hard to understand; and diseases, in general, are complicated. In 2005, there are no *perfect* drugs.

Q: Where does this new info come from and how does it affect YOUR healthcare?
A: Scientists continue to study how diseases affect

the body. They also study how the body fights back. Scientists try to answer specific questions about a disease or drug by designing a study or **"clinical trial."** Meetings to present and discuss the results of studies are called **"scientific conferences."** The kinds of people who might attend conferences are: scientists, people who provide healthcare such as doctors and nurses, **"patient advocates,"** and the press. There are different reasons that scientists design clinical trials. Sometimes it is to find out about how effective a new drug is to gain approval from the Food and Drug Administration (FDA) so it can be available as quickly as possible. Sometimes it is to study if an older drug is causing serious side effects in large numbers of people. Whatever the reason, these studies often have an impact on certain groups of people, and we're here to show you how new studies might affect you, your friends, peers or family. See our "Helpful Tools" section to read more about how we do this.

Q: What happens at conferences?

A: The major HIV science conferences are like big games of medical "show and tell" that happen several times a year. Some information presented at conferences (study results) is very important. But some results don't really mean anything, mostly because the clinical trials were not designed very well in the first place. There are things to look out for and questions to ask when looking at study results that will tell you how much you can rely on the information. Good, bad, or indifferent, the results from studies need to be looked at carefully so we can pull out the best info and add it to the knowledge we already have. If you take part in the process by regularly reading this newsletter, it may improve your HIV healthcare by helping you enter into a more active relationship with your healthcare provider.

Looking for Treatments That Last

If something lasts, whether it is a good pair of shoes or an anti-HIV drug, it is said to be **“durable.”**

Knowing that a new drug is durable is very important because we have moved from an era of trying to keep people with AIDS alive for a few more months to a time of life-long treatment and a focus on a good quality of life. To really know if a new (or existing) drug can be safely used over a long period of time, we need long-term studies and follow-up. When you see a conference report, pay careful attention to how long the study lasted. Companies are often eager to report early results that look good, and may report results after only 24 weeks (6 months). This is especially true if the company is a small biotech firm that needs to show good results to raise money or attract a larger pharmaceutical company to pay for the rest of the cost of bringing the drug to market. It's important to look for 48-week (one year) data and what's even better is 96-weeks (two years) or longer.

In Glasgow, we were glad to see the results from two studies that were longer than you often see:

Clinical Trial:

Study 720

The results of this trial presented in Glasgow were based on a really long study—**312 weeks** (6 years!)—that continues to follow a group of **“treatment naïve”** people who are taking a boosted PI regimen (see **“PI boosting”**) that contains Kaletra and two **“nukes.”** The results showed that Kaletra plus two nukes are able to keep HIV under control for a large percentage (62%) of the people in the trial. It also showed that (1) the T-cells of these people increased a lot no matter how many T cells they started with and (2) that no resistance to **“protease inhibitors (PIs)”** was seen in people when the amount of HIV in their body started to increase. It was usually the nukes that started to fail.

Clinical Trial:

Study BMS 045

The **96-week** results from this trial comparing the protease inhibitors, Reyataz and Kaletra, were also presented in Glasgow. The **“PI booster,”** Norvir, was used in both **“regimens”** to boost the amount of PI in the blood stream [Note: Norvir is already contained in the Kaletra pill, but has to be added separately to other PIs like Reyataz]. The same two nukes were also taken with both the PIs. The study results showed that boosted Reyataz plus two nukes is **“non-inferior”** to the regimen of Kaletra plus two nukes. The results presented also showed that people taking the Reyataz regimen had lower levels of cholesterol and less chance of getting diarrhea, but more chance of yellowing of the eyes and skin (jaundice) than those taking Kaletra.

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D Results based on **“data”** from longer trials is definitely the way to go!
TN But the number of weeks a trial runs is not all we need to look at. It is also good to look at (1) how many people started the trial versus how many finished it (the more people, the better!) and (2) the complete “resistance” information on all the people who did finish the trial.

The **312-week** Kaletra study (720) is a good example of a trial that reported on all of these things. On the other hand, the types of studies that compare regimens (head-to-head), such as the **96-week** study described above (BMS 045), usually need to include more patients than were in this trial. It is also good to look at the number of people who didn't finish a trial—and their reasons for not finishing—because trial results can be pushed one way or another by drop-outs, preventing us from seeing the entire picture. For example, if

someone drops out of a trial because their HIV came back, this is different than leaving the trial because of side effects or convenience. Information related to why people did not finish was not presented. Investigators were allowed to define treatment failure themselves rather than having a set of conditions supplied for them. When this is allowed, we don't know if each investigator's definition of failure was exactly the same or not. These details are especially important because they can bias the study in favor of, or against, either drug.

Another way to look at how well a new regimen is really doing is to know how resistant a person's HIV was before they even started the new regimen. Because mutated virus fades and **“wild type virus”** quickly returns when a drug is stopped, it is important for a person to actually be taking a drug in order to measure resistance to it. A lot of people (60%) on the BMS 045 trial were not on PIs when the

first resistance testing was done so it is hard to say if these people had HIV that was a little—or very—resistant to PIs in the first place. This makes it very difficult to know (1) what type of resistant HIV the new regimens were actually fighting, and (2) if the resistance was evenly distributed between the two regimens. Without this information, it is hard to make a head-to-head or “apples-to-apples” comparison.

Because anti-HIV meds often affect the amount of fat in the blood (cholesterol), trials often measure it. In this trial, they looked at % of change from where participants' cholesterol levels started on entry in the study. The only difference of note was in the total **“cholesterol”** and triglycerides. These went up more in the people who were in the Kaletra arm than in the Reyataz arm, but there was little difference in LDL and HDL (bad and good types of cholesterol).

Update: Salvage Therapy

There were several presentations on the topic of “salvage therapies.” One was from **The Forum for Collaborative HIV Research** (“the Forum”). The Forum is a partnership of government agencies, the pharmaceutical industry, HIV researchers, healthcare providers, and the HIV patient community (for more information on the Forum, go to <http://www.hivforum.org>). It sponsors different workshops where leaders working in the field of HIV discuss how to improve HIV research. Dr. Veronica Miller directs the Forum. At a recent Forum meeting, Dr. Miller gave a presentation on how best to do research on HIV salvage therapies and the importance of designing new trials that control HIV that has already developed **“resistance”** to older anti-HIV drugs. The following is a summary from Dr. Miller’s presentation:

There is a real need to study more than one new drug at a time because salvage patients should not add just one drug to their current regimen because of a high risk of failure. Ideally, they would have at least two new drugs to use. But, if new drugs are studied only one at a time, people may not be able to rely on clinical trials for their next treatment. To be safe, they’ll have to wait until at least one new drug is approved, and then try to get into a trial of a 2nd new drug. Patient advocates want researchers to study two new drugs within the same clinical trial. There are ways to design these trials so that the benefits and risks of each new drug can be sorted out. Based on earlier work presented to the FDA by the Forum, the FDA has agreed to accept the results of this type of trial.

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ST Unfortunately, for scientists to research two new anti-HIV drugs

TE at the same time, the drugs would need to be at roughly the same stage of development—which does not happen very often. In addition, if the drugs are being produced by two different companies, both will have to be willing to get together and agree about the trial’s design and how it is run. Agreeing on design is important to them because they will each want to use the results of the trial to get their drug approved. This kind of agreement between companies is a rare occurrence! Dr. Miller ended her presentation by pledging that the Forum will continue to try to work with experts to find answers to support this process.

New HIV Drugs

Almost every conference has a session on the anti-HIV drug **“pipeline,”** which is of particular importance to people who are running out of anti-HIV drugs (see **“salvage therapy”**). Several NEW **“nukes”** were talked about in Glasgow (unabstracted talk PL13.1). Some of these are very similar to existing drugs and are called **“me-too drugs.”** They may be a little better in terms of side effects or needing to be taken fewer times (once a day). Other new nukes are really **“second generation”** nukes, which provide control of HIV that is already resistant to existing nukes. Among nukes in development, the cytidine analog D-d4FC is furthest along.

NEW **“non-nukes”** coming (such as Capravirine from Pfizer and TMC-125 from Tibotec) offer the hope of controlling HIV that is already resistant to the existing non-nukes.

Of the NEW **“protease inhibitors,”** tipranavir is very close to shooting out of the pipeline and being approved by the FDA. Results of the “RESIST-2” study about tipranavir were presented at the end of the conference as a **“late breaker”** (**“Abstract”** PL 14.3). Late breakers are often the most exciting presentations. Tipranavir is being developed by the pharmaceutical company, Boehringer Ingelheim. The same study design was used in two different parts of the world. (The one that took place in North America was called “RESIST-1.”) In Europe and Latin America, it was called

“RESIST-2.” Only very HIV **“treatment experienced”** people took part in this trial. They had to have already taken drugs in three of the four anti-HIV classes and to have virus with at least one important change (resistance mutation) causing PIs to work

Of the NEW protease inhibitors, tipranavir is very close to shooting out of the pipeline.

less well. The participants were selected by chance (randomized) to receive either tipranavir plus a small dose of Norvir (200 mg) to boost it or another Norvir-boosted protease inhibitor. Drugs were not chosen for these people until a resistance test of the HIV in their blood was done. Resistance test results help the researchers know which PI might be their best shot at success. The people in the trial could also start using the drug Fuzeon (T-20), a fusion inhibitor, along with tipranavir. Fuzeon belongs to the new fusion inhibitor class of anti-HIV drugs and can be effective against virus that is resistant to any drug from the other classes. Results showed that (1) people taking tipranavir did

better than those taking the other “best shot at controlling HIV” boosted regimens, and (2) the best results occurred if tipranavir was combined with a couple of drugs the patients were not resistant to, or combined with Fuzeon. [Note: TMC-114, a PI from Tibotec, along with drugs in new classes. **“integrase inhibitors”** and **“maturation inhibitors”** are further back in the pipeline and will take longer to become available.]

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Drugs that help people fight resistant virus are really needed, and the results from the RESIST-2 study show that tipranavir will be a welcome addition. There are two types of resistance tests used to guide treatment: (1) a genotypic (*gee-noh-tip-ick*) test that looks for changes (mutations) in the virus that predict resistance, and (2) a phenotypic (*fee-noh-tip-ick*) test that measures how a person's HIV acts in the presence of drug. Because we know that a mutated (resistant) HIV virus fades and "**wild type**" virus quickly returns when a drug is stopped, it is important for

person to actually be taking a drug in order to measure resistance to it. In this study only one kind of resistance test (genotype) was run on people before starting the study. We would have liked to see phenotypic information on the people who took part in the study. When the researchers looked back at some of the people who had phenotypic tests before they started on the study, they found a high level of resistance to several PIs. Although it's a good study, having this information at the start would have helped the researchers yield even more reliable results.

Your opinion counts!

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Liver Issues

At some conferences, including the Glasgow conference, several presentations are overviews or recaps of a topic. One such presentation (Abstract PL14.1) dealt with liver problems in people receiving HIV treatment. A German physician noted that a major reason for stopping or changing anti-HIV therapy is liver toxicity (hepatotoxicity). It can be caused by (1) nukes, (2) the non-nuke, Viramune, and to a lesser extent Sustiva (3) by protease inhibitors. He laid out when the problems normally show up and what we know about the causes:

Drugs	When problems occur	How problems are caused
Nukes	More than 6 months after starting drugs	Damage to the " <i>mitochondria</i> "
Non-nukes (especially Viramune)	Either during the first 4 weeks (for Viramune) or gradually increasing with time on drug	" <i>Hypersensitivity reactions</i> " and/or too-high drug levels
Protease inhibitors	Gradually increasing with time on drugs	Unknown

Liver problems are growing in importance for people with HIV, partly because of longer life spans. This is especially true for people who are both infected with "**hepatitis**" (B or C) along with HIV. When someone has both HIV and hepatitis, we call them co-infected.

Liver problems are difficult to treat and can be very serious. In some groups of HIV-positive people, liver problems are the leading cause of death. HIV physicians will have to learn how to minimize liver problems caused by HIV medications, and how to treat them when they occur.

The more liver damage (fibrosis/cirrhosis) people have, the more trouble they may have with liver problems related to their HIV medications. In this European trial, 107 people co-infected with HIV and hepatitis C who had liver biopsies (the only real way to measure fibrosis or cirrhosis) were studied. People with more severe fibrosis had higher levels of liver enzymes too, which shows that the liver is working too hard. Most of the people studied were taking non-nukes. The only differences between the non-nukes, Sustiva and Viramune, showed up in people with a lot of liver damage. In these people, Viramune was more likely to cause damage, followed by Sustiva. The rate of damage for people taking anti-HIV therapy that did not contain non-nukes was less than half of the rate showed by Sustiva.



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LH Although studies like these are now a part of every major HIV conference, these studies were underpowered to answer certain vital questions. Future research should focus in these questions: (1) What happens to the health and quality of life of co-infected people on anti-HIV therapy in the long-term? (2) What effect does having raised liver enzymes for a long time have? (3) Which drugs affect the rate of liver damage and at what point does it start?

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