



P.I. Perspective

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NEWS ON APPROVED ANTIRETROVIRALS

Switch to Viramune safe for some who can't tolerate Sustiva

A poster found that it was generally safe to substitute Viramune (nevirapine) for Sustiva (efavirenz) when people were experiencing unacceptable side effects. The study, while small, may help provide options for some people who cannot tolerate Sustiva but wish to avoid using a protease inhibitor (PI).

Use of Viramune, an NNRTI like Sustiva, has been limited mostly due to its uncommon but potentially severe drug reactions. Women with CD4 counts above 250 and men with counts above 400 are generally discouraged from starting a regimen with Viramune due to a higher risk of catastrophic liver damage. Like Sustiva, Viramune has been shown to cause a rash in some people. Unlike Sustiva, it has not been shown to change levels of blood fats.

While Sustiva is widely used and generally well tolerated, some people are unable to tolerate it due to side effects. The most common ones are central nervous system (CNS) effects like dizziness and sleep disturbance as well as rash. Some people with a history of substance dependence find Sustiva's mild CNS effects particularly troubling.

HIV therapy that includes PIs is most commonly given to people who can't tolerate Sustiva. Some people wish to avoid PIs due to their risk of both short- and long-term side effects, including gastrointestinal distress and elevated risk of heart disease.

The study presented looked at people who had taken Sustiva in the ACTG 5095 study, who could not tolerate it due to side effects. Overall, 75 people (55 male and 20 female) switched to Viramune. 85% of people who switched due to CNS effects improved after switching, while 15 of 18 had their rash improve. Six people had rash while taking Viramune, and 14% had liver problems after the switch compared to 6% of those who didn't switch. Most people who switched maintained good control over their HIV.

This study suggests switching to Viramune may be a safe option for some people who cannot tolerate Sustiva. The risk of drug-related liver problems is greater for women and people with high CD4 counts (women >250, men >400) when starting Viramune, so it should be used with extreme caution in these people.

CONTENTS

- 1–10 Approved HIV drugs
- 11–13 Experimental HIV drugs
- 13–15 Opportunistic infections
- 15–17 HIV-related conditions
- 17 Cure based research
- 18–20 News briefs

NEWS ON APPROVED ANTIRETROVIRALS

Study shows people can safely switch to Atripla

Results from a study found that people on a stable, suppressive HIV regimen can maintain control of their HIV if they switch to the fixed-dose pill Atripla (efavirenz + tenofovir + emtricitabine/FTC). The same study also found a somewhat higher risk of side effects for those who switched.

In this study, 300 people with undetectable HIV on a stable regimen were randomly assigned (2:1) to either switch to Atripla or stay on their same regimen. In all, 207 people were picked to switch, and 97 stayed on their current regimen. The study evaluated HIV levels as well as the frequency and type of side effects experienced.

Both strategies worked quite well. After 48 weeks, 87% of people who switched to Atripla had HIV levels <50, compared to 85% of people who stayed on their regimen — a difference not considered to be statistically significant. CD4 counts stayed stable, raising only a small amount in both.

People who had taken an NNRTI before were somewhat more likely to stay undetectable if they switched, while those who had taken protease inhibitors were somewhat more likely to stay undetectable if they stayed on their old regimen. The differences between these groups were small and appeared to be due mostly to people who were lost to follow up during the study.

Significantly more side effects were reported by those who switched. First, people had been on their old regimens for at least 3 months, with an average time on their pre-study regimen of 2.5–3 years. Side effects are always more likely when switching from a well tolerated regimen to any new regimen. Secondly, most of the side effects reported were typical of efavirenz, including dizziness and sleep disturbances. Few people stopped their regimens due to side effects — a fairly reliable measure of tolerability.

Over 90% said they would prefer to take a regimen as one pill once a day. 97% of those on Atripla said their regimen was easy to take, compared to 81% who didn't switch. Adherence was high in both groups, with no meaningful difference. Atripla is the most common HIV drug combination for first line therapy. This study suggests it can also be used safely by people who have taken other regimens looking for a simpler one.

drug i.d. chart

TRADE NAME	GENERIC NAME
Protease inhibitor	
Agenerase	amprenavir
Aptivus	tipranavir
Crixivan	indinavir
Invirase	saquinavir
Kaletra	lopinavir + ritonavir
Lexiva	fosamprenavir
Norvir	ritonavir
Prezista	darunavir
Reyataz	atazanavir
Viracept	nelfinavir
NRTI (nucleoside) and NtRTI (nucleotide) analogue reverse transcriptase inhibitor	
Combivir	lamivudine + zidovudine
Emtriva	emtricitabine (FTC)
Epivir	lamivudine (3TC)
Epzicom	lamivudine + abacavir
Retrovir	zidovudine (AZT)
Trizivir	lamivudine + zidovudine + abacavir
Truvada	emtricitabine + tenofovir
Videx	didanosine (ddI)
Videx EC	ddI enteric-coated (ddI EC)
Viread	tenofovir
Zerit	stavudine (d4T)
Ziagen	abacavir
NNRTI (non-nucleoside) reverse transcriptase inhibitor	
Intelence	etravirine
Rescriptor	delavirdine
Sustiva	efavirenz
Viramune	nevirapine
NRTI + NNRTI combination	
Atripla	efavirenz + emtricitabine + tenofovir
Entry inhibitor	
Fuzeon	enfuvirtide (T20)
Selzentry	maraviroc
Integrase inhibitor	
Isentress	raltegravir

NEWS ON APPROVED ANTIRETROVIRALS

Study explains Isentress' excellent resistance profile

A presentation helps deepen our understanding of Merck's integrase inhibitor, Isentress (raltegravir). The talk by Daria Hazuda showed how resistance develops to Isentress and poses a possible explanation for its unparalleled ability to reduce HIV levels quickly.

Hazuda reported on an analysis of the BENCHMRK 1 and 2 studies, which were the basis for Isentress' FDA approval. In these studies, people with extensive experience taking HIV drugs were randomly assigned to take either Isentress or a placebo, each taken with *optimized background therapy* (or the best available combination of HIV drugs chosen with the aid of resistance testing).

Overall it was rare to develop resistance to Isentress in these studies. When people did, they tended to develop mutations that had been seen in earlier research, particularly at positions 148 and 155. This analysis found that over time people tended to accumulate more resistance mutations, and the pattern of mutations tended to evolve from mostly 148 to mostly 155. This may be important, as the 155 mutation is more damaging to HIV's ability to replicate, called *viral fitness*, than 148.

Perhaps of more interest is the likelihood that experiencing treatment failure on Isentress was not related to concentrations of the drug measured in the blood. Rather, it seems to be related to the amount of time the drug remains bound or attached to the integrase enzyme, called its *off-rate*.

It appears that Isentress, and other integrase inhibitors, stay attached to the integrase-HIV complex longer than they are measurable in the blood. This may explain why Isentress reduces HIV levels more quickly than other HIV drugs, as it retains activity longer than it is measurable in the blood.

Isentress has proven a very successful option for many people with few HIV treatment options. Resistance to Isentress remains rare, but this study helps us better understand how it does develop as well as its unique ability to reduce HIV levels more quickly than other drugs.

NEWS ON APPROVED ANTIRETROVIRALS

96-week data from CASTLE study presented

A poster found that after 96 weeks more people taking Reyataz (atazanavir) boosted with Norvir (ritonavir) once daily had HIV levels below 50 copies compared to those taking Kaletra (lopinavir + ritonavir) twice daily. The study also found similar rates but different types of side effects for these two widely used protease inhibitors (PIs).

The CASTLE study looked at almost 900 people taking HIV drugs for the first time, randomly assigned to take either boosted Reyataz once a day or Kaletra twice a day, both combined with Truvada (tenofovir + emtricitabine/FTC). 31% of people were female and the average CD4 count at the start of the study was around 200. The study was designed to compare the proportion of people with HIV levels below 50 copies, as well as the frequency and types of side effects reported.

After 96 weeks, 70% of people taking boosted Reyataz had HIV levels below 50 copies compared to 63% of those on Kaletra. This difference was due to the higher rates of those who stopped taking Kaletra. When they were excluded from the analysis, 89% of those on Reyataz had undetectable HIV vs. 88% on Kaletra. People taking Kaletra had somewhat larger increases in CD4 counts, with an average gain of 290 cells compared to 268 for Reyataz.

There were similar rates of side effects reported by both groups, but the types were quite different. Overall, 14% of people taking Reyataz reported a significant side effect compared to 11% taking Kaletra. Those on Reyataz experienced elevated levels of bilirubin and jaundice more often while those taking Kaletra reported more diarrhea and other gastrointestinal (GI) symptoms.

There are two important caveats. First, Kaletra is now widely used once daily when used in first line therapy. Second, the older soft gel form was used by most people in the study. The newer tablet form might cause GI problems somewhat less frequently, although the data are not completely clear.

Reyataz is listed as a preferred option for first line therapy in the Federal Guideline and has surpassed Kaletra as the best selling PI in the US. This study supports using boosted Reyataz as part of a person's first HIV regimen. Another poster from this study (www.projectinform.org/news/08_icaac/102708.shtml) was presented.

NEWS ON APPROVED ANTIRETROVIRALS

CASTLE analysis finds no benefit for once daily dosing

A poster suggests that there is no adherence benefit of protease inhibitor treatment given once a day compared to twice a day. In fact, once daily dosing seemed to lead to small increases in forgotten doses. With many drug companies convinced that once daily treatment is easier to market to people with HIV, this study suggests it does not lead to better adherence.

The poster looked at adherence to treatment in the CASTLE study, which compared once daily Reyataz (atazanavir) boosted with Norvir (ritonavir) to twice daily Kaletra (lopinavir + ritonavir). They both were taken with Truvada (tenofovir + emtricitabine/FTC).

Overall, adherence rates were above 80% throughout the study and did not differ between the two groups. While these rates to Reyataz dropped somewhat more (88% to 82%) than Kaletra (86% to 84%), the difference is not significant. Interestingly, more people reported forgetting to take Reyataz (11%) than Kaletra (6%). This suggests, but does not prove, that there might be a marginal benefit to twice daily dosing in terms of forgotten doses.

There were somewhat higher rates of people stopping Kaletra. After 48 weeks, 91% of people were still taking Reyataz compared to 86.5% of those on Kaletra. This difference is small, but it suggests a possible small benefit in terms of tolerability for once daily dosing. This difference could be due to the drugs themselves rather than how often they were taken each day.

Over the past few years, once daily HIV regimens have become more common particularly since the introduction of Atripla (efavirenz + tenofovir + emtricitabine/FTC), the first full HIV regimen that's taken as one pill once a day. While people with HIV commonly express a preference for simpler regimens, there's little comparative data to show how well they perform compared to twice daily regimens. This CASTLE analysis suggests that once daily dosing does not lead to better adherence and might actually lead to slightly higher rates of forgotten doses.

NEWS ON APPROVED ANTIRETROVIRALS

Large study supports earlier treatment

A large study found that people who delayed starting HIV treatment until their CD4 counts fell below 350 were 70% more likely to experience a new AIDS-defining illness or death, compared to those who began at CD4 counts of 350-500. This finding adds to the growing body of evidence supporting earlier treatment of HIV disease.

The researchers looked at the medical records of over 8,000 people from 22 research cohorts in the US and Canada from 1996 to 2006. Of those, almost 2,500 started HIV treatment with CD4 counts of 350-500, with the rest delaying treatment until sometime after their CD4 counts fell below 350. Current US guidelines recommend treatment for anyone with a CD4 count <350.

Overall, people who started with lower CD4 counts were 1.7 times as likely to experience an AIDS-defining illness or death. Interestingly, the researchers found that neither a history of injection drug use nor HCV co-infection changed the increased risk associated with delayed treatment, although they did lead to more frequent illness and death overall. Not surprisingly older age was independently associated with an increased likelihood of illness or death, with each decade adding a 60% risk.

The researchers had no way of directly measuring adherence to treatment. They did look at the likelihood that people in each group had undetectable HIV levels once they began treatment and found no significant difference between the groups.

Being a retrospective, combined cohort analysis limits the strength of this study's observation. The presenters acknowledged this, and they said they took great pains to control for the kinds of biases that might influence their findings. The same research team is analyzing this database to compare the rates of AIDS-defining illness and death between people who start HIV treatment with CD4 counts above and <500. They expect to present those results soon.

In spite of the limitations of this kind of study, its findings are nonetheless important. Lacking a definitive, prospective, randomized study to answer this question, these studies may influence guidelines and prescribing practices.

NEWS ON APPROVED ANTIRETROVIRALS

Two studies look at Intelence

Two posters looking at the new NNRTI Intelence (etravirine, TMC-125) were presented. One study found that the amount of time it took people to achieve full control of HIV while on Intelence did not affect how long their regimens continued to work. Another poster showed that fewer people taking Intelence compared to placebo experienced an AIDS-defining illness or death.

Intelence was approved in January 2008, based on data from the DUET 1 and 2 studies, which showed it to be superior to placebo in terms of reducing HIV levels and increasing CD4 counts. Each study group also took Prezista (darunavir) boosted with Norvir (ritonavir).

The first poster looked at whether there was a relationship between how quickly people in the DUET studies achieved HIV levels below 50, and how likely they were to maintain viral control after 48 weeks. A total of 599 people who took Intelence in DUET 1 and 2 were divided into 3 groups: 281 people who reached HIV levels below 50 within 12 weeks, 104 people who became undetectable in 12-24 weeks, and 214 people who did not become undetectable within 24 weeks.

In a conservative, *intent-to-treat* analysis (which counts people who leave the study or are otherwise lost to follow-up as treatment failures), 87% of people who reached undetectable within 12 weeks stayed so at 48 weeks, compared to 86% of people who reached undetectable in 12-24 weeks. Only 14% of people who hadn't achieved HIV levels below 50 by 24 weeks were undetectable at 48 weeks.

The relationship between the speed of viral load reductions and the durability of treatment has been raised recently due to studies which found that Sustiva (efavirenz) reduces HIV levels faster than Intelence, while Isentress (raltegravir) reduces them faster than Sustiva. This study suggests that the speed at which someone responds to treatment with Intelence does not predict if they are likely to maintain good viral control after 48 weeks.

A second study looked at the rates of AIDS-defining illnesses and death in people on Intelence compared to placebo in the DUET studies. This analysis is crucial, as approval of Intelence was based mostly on surrogate markers, like HIV levels and CD4 counts, rather than its impact on HIV disease.

Slightly over 1,200 people from DUET 1 and 2 were studied. There were 59 AIDS-defining illnesses or deaths (9.8%) for those on placebo compared to 35 (5.8%) for people taking Intelence. The difference was larger when people in the placebo group taking Sustiva for the first time were excluded.

These two studies, combined with earlier results, show that Intelence is an effective treatment option for people with experience taking HIV drugs. Intelence is the first second-generation NNRTI, and it's important because unlike other NNRTIs it is able to overcome resistance to other NNRTIs like Sustiva and Viramune (nevirapine). There is very limited data on using Intelence with protease inhibitors other than Prezista.

NEWS ON APPROVED ANTIRETROVIRALS

More Kaletra monotherapy results

Two posters presented follow-up data from two small studies of the boosted protease inhibitor (PI) Kaletra used as monotherapy. While most people taking Kaletra alone were able to maintain good control of HIV replication, the rates of failure were higher than those seen in recent studies of traditional three-drug combinations.

The IMANI-2 study was an open label, single arm study of people taking Kaletra alone as their first HIV regimen. Earlier results found 79% of people with HIV levels below 75 copies after 48 weeks. This poster presented follow-up results after 96 weeks.

After 96 weeks, 74% of people had HIV levels below 75 copies. Four had detectable levels of HIV, with three of those being below 1,000 copies. Twelve had detectable HIV levels at some point in the study, which returned to below 75. The authors speculated this was due to adherence issues. Importantly no primary PI mutations were detected in people with replicating HIV.

Another poster looked at three years of follow-up from the OK04 study, which compared Kaletra monotherapy to a traditional HAART regimen of Kaletra + 2 NRTIs. Results from an earlier time point found Kaletra monotherapy to be equivalent to Kaletra + 2 NRTIs after 96 weeks. A published paper from this study in the Journal of AIDS showed that while significantly more people taking traditional three-drug HAART had HIV levels below 50 at 48 weeks (95% vs. 81%), the difference was not quite large enough to be considered inferior.

This poster looked at a total of 100 people who were followed for 144 weeks after being randomized to take Kaletra alone in OK04. Of those, 70% continued to have HIV levels below 50 copies. Most who had HIV levels rise during the study were able to re-suppress HIV replication by adding 2 NRTIs.

Studies of traditional three-drug HAART regimens conducted years ago often saw similar rates of people with HIV levels below the limit of detection: around 70%. While study-to-study comparisons are always problematic, most studies of HAART regimens conducted these days result in higher rates of treatment success, more in the neighborhood of 80–90%.

While the authors of these two posters claim their results support larger studies of Kaletra monotherapy, Project Inform believes they show that Kaletra monotherapy is less likely to fully suppress HIV replication than Kaletra + 2 NRTIs, and it does not merit further study. We feel further study of this strategy is likely to put volunteers at an unacceptably high risk of treatment failure.

NEWS ON APPROVED ANTIRETROVIRALS

Four posters add to our knowledge of Lexiva

Several posters showed results on the use of the protease inhibitor (PI), Lexiva (fosamprenavir). The studies looked at long-term follow-up from the KLEAN study, as well as 3 studies investigating different dosings of the drug. Lexiva is recommended by the Federal Guidelines as a preferred PI when boosted with Norvir (ritonavir) as part of a person's first HIV regimen. The drug can also be used without Norvir by people who have never taken PIs.

The first poster was an analysis of long-term results from KLEAN. This was a head-to-head comparison of boosted Lexiva to Kaletra (lopinavir + ritonavir) both taken with the fixed dose combination pill Epzicom (abacavir + lamivudine/3TC). Results from KLEAN have been presented at various conferences. This is the first presentation of results after 144 weeks.

The results were mostly good for Lexiva. After 144 weeks, 83% of people on Lexiva had HIV levels <400 copies, compared to 70% on Kaletra. An even larger difference was seen when looking at the proportion of people with HIV levels <50, with 77% for Lexiva and only 55% for Kaletra.

On average people taking Kaletra did gain more CD4 cells, averaging 335 compared to 300 for Lexiva. This is the latest in a number of studies that have shown Kaletra to be somewhat better than other HIV drugs in terms of increasing CD4 counts.

There were also more side effects among people taking Lexiva. Overall, 42% on Lexiva reported some side effect compared to 27% for Kaletra. There was no difference in more serious grade 3 or 4 adverse events, with 24% for Lexiva vs. 23% for Kaletra.

The second poster reported on efficacy and side effects of two dosing schedules for Lexiva. Just over 200 people were studied, with half taking 1,400mg Lexiva + 100mg Norvir once a day, and the others taking 700mg Lexiva + 100mg Norvir twice daily. Everyone also took Epzicom.

Two dosing methods were equally good at reducing HIV levels. After 24 weeks, 73% on Lexiva once daily had HIV levels below 50 copies, compared to 76% taking it twice a day. People on Lexiva once a day gained slightly more CD4 cells, averaging 114 compared to 99 for the twice a day group.

There were some differences in terms of side effects. Overall, 22% of the once daily group reported side effects, compared to 31% in the twice daily group. There was more diarrhea and greater changes in blood fats among people taking Lexiva twice a day. This difference might be due to the

higher amount of Norvir taken. Hypersensitivity reactions were somewhat more common in the once daily group. HLA testing, which accurately predicts the risk of this reaction.

The next study looked at the risk of resistance in people who saw their HIV levels rise while taking one of two doses of Lexiva: 1,400mg + either 100 or 200mg Norvir, once a day each along with Epzi-com. There was no evidence of PI resistance in people who met the criteria for virologic failure.

The last poster was an analysis of the same study that compared the safety and efficacy of those two doses of Lexiva. After 96 weeks, significantly more people taking 100mg Norvir + Lexiva had undetectable HIV: 78% vs. 53%. There was no difference when people who left the study or were lost to follow-up were excluded. This shows that the difference was likely due to tolerance issues rather than potency. However, there were no major differences in the rate or type of side effects reported.

While none of these studies add much to our understanding of Lexiva, they do augment the evidence that it's a potent and well tolerated option for people wanting to take a boosted PI. A few years ago, Kaletra stood alone as the preferred boosted PI. Now a number of head-to-head studies have shown most of the widely used PIs are equivalent to Kaletra, including Lexiva.

NEWS ON APPROVED ANTIRETROVIRALS

Switching Combivir to Truvada keeps HIV undetectable, improves blood fats, fails to improve limb fat

A study found that people who switched from Combivir (zidovudine/AZT + lamivudine/3TC) to Truvada (tenofovir + emtricitabine/FTC) maintained their control of HIV replication, had improvements in blood lipids, but did not see improvements in limb fat.

The poster presentation showed results from a 48-week continuation of the earlier 934 study. That study lasted 144 weeks and compared Combivir to Truvada, both taken with Sustiva (efavirenz). In 934, people taking Combivir could switch to Truvada or stay on Combivir after 144 weeks.

After 48 weeks, similar proportions of people in both groups had HIV levels below 50: 94% for Truvada and 90% for Combivir. On average, people who switched to Truvada gained 9 CD4 cells compared to an average loss of 6 for those who stayed on Combivir.

People who switched to Truvada experienced small improvements in their measures of blood fats. While HDL levels (good cholesterol) remained virtually unchanged in both groups, levels of LDL (bad cholesterol) and triglycerides declined more in people who switched.

Unfortunately, people who switched did not regain lost limb fat. In the first phase of the study, significantly more people taking Combivir lost limb fat, compared to those on Truvada. However, 48 weeks after the switch, there were no significant changes in either group.

This study supports other data showing that Truvada is superior to Combivir. Combivir was downgraded from preferred to alternative in the Federal Guidelines, in part due to the earlier results from 934. This continuation study shows that when people switch from Combivir to Truvada they are likely to maintain undetectable levels of HIV, might experience small benefits in blood fats, but are unlikely to see improvement in lost limb fat.



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NEWS ON APPROVED ANTIRETROVIRALS

Study supports use of Isentress for first line treatment

A study found that Isentress (raltegravir) was equally potent and better tolerated than Sustiva (efavirenz) when used as part of first line therapy. While it's unlikely to greatly change prescribing practices, this study adds to the list of impressive results for Merck's first-in-class integrase inhibitor.

The STARTMRK trial randomized 563 people who had never taken HIV treatment to take either Isentress or Sustiva, both combined with Truvada (tenofovir + emtricitabine). The study was designed to compare the proportion of people with CD4 counts below 50 and the rates of adverse events (side effects). Data were presented after 48 weeks.

Overall, similar proportions of people in both groups had CD4 counts below 50: 86% for Isentress vs. 82% for Sustiva. More people (12.4% vs. 8.5%) stopped taking Sustiva during the study, which is considered a good measure of a drug's tolerability. As seen in other studies, people taking Isentress saw their HIV levels decline more quickly than those on Sustiva.

People taking Isentress had somewhat larger increases in CD4 counts as well, averaging 189 cells compared to 163 for Sustiva. This difference is considered statistically significant (meaning it is unlikely to be from chance), but the impact of such a difference on HIV disease progression or other health outcomes is unclear.

People taking Sustiva in this study were more likely to experience side effects. 77% of people taking Sustiva reported drug-related side effects, compared to 44% of people on Isentress. Central nervous system effects, like dizziness and sleep disturbances, along with rash made up most of the difference.

While this study shows that Isentress is equally potent and better tolerated than Sustiva when either is taken with Truvada as part of first line therapy, it may be unlikely to significantly change prescribing practices. Isentress is taken twice a day while Sustiva is once daily. Research shows some preference on the part of patients for once-a-day treatment. Merck is studying the potential to give Isentress once daily, but those results are not yet available. Also, Sustiva + Truvada are sold together in the very popular once-a-day pill Atripla. Its simplicity and potency has led it to be the most prescribed combination for first line treatment in the US.

Lastly, Sustiva has been on the market for many years now and has built up a large amount of safety information. At a meeting Project Inform held just before ICCAC, one widely respected HIV doctor and researcher cautioned those in attendance against what he sees as Americans' tendency to jump on the newest thing, reminding everyone that there is no substitute for real world experience when it comes to understanding the safety of a drug. "How many side effects did we learn about only after a drug was approved?" he reminded us.

While this study might not unseat Atripla as the market leader for first line treatment, it helps support the use of Isentress earlier in the course of HIV disease. Isentress was studied initially for use in people with extensive HIV treatment, where it has worked quite well. This study suggests that Isentress can be successfully used as part of earlier HIV drug combinations as well.

NEWS ON APPROVED ANTIRETROVIRALS

More sensitive test leads to better results for Selzentry

A re-analysis of the MERIT study using the second generation Trofile test was presented. The poster presentation by Michael Saag MD found that Selzentry (maraviroc) was comparable to Sustiva (efavirenz) when used as part of a person's first HIV regimen.

The poster, titled MERIT ES, looked at data from the MERIT study that was presented at the International AIDS Society meeting in Sydney in 2007. That study found that Selzentry failed to match up to Sustiva, when either was taken with Combivir (zidovudine/AZT + lamivudine/3TC). Oddly, a planned analysis showed that the difference was due to significantly lower rates of success in people taking Selzentry in the southern hemisphere compared to those in the northern hemisphere.

To understand this unusual finding, the investigators took a second look at these results using an enhanced Trofile test, which determines whether a person's HIV uses only the CCR5 co-receptor (*R5-only*) to gain entry into cells or can use another receptor, CXCR4 (*X4*). The new test can detect lower levels of *X4* HIV and therefore might better predict success when using an *R5* drug like Selzentry. Another study (www.projectinform.org/news/08_icaac/102608c.shtml) presented found increased success rates of another *R5* drug, vicriviroc, when the new test was used.

In the MERIT ES re-analysis, 15% of people of people who were determined to have *R5-only* HIV were found to have HIV that could use *X4*. This included those with either a mixed population or a dual virus that can use either co-receptor. There were similar numbers in people randomized to take Selzentry or Sustiva.

When that 15% of volunteers was removed from the analysis, Selzentry proved to be equal to Sustiva in terms of reducing HIV levels and superior in terms of tolerability. After 48 weeks, 68% of people from both groups had HIV levels below 50 copies. On average, people taking Selzentry gained 174 CD4 cells compared to 144 for those on Sustiva.

Overall, 13% of people taking Selzentry reported any adverse event compared to 43% of people taking Sustiva. The difference was due mostly to more frequent central nervous system reactions and rash among people on Sustiva.

This result is good news for Selzentry. Although not specifically addressing the issue of the different response rates between hemispheres, the overall similar rates when using the new more sensitive Trofile test make that observation most likely the result of higher rates of undetected *X4* HIV in the southern hemisphere.

While this result is positive for Selzentry and its maker Pfizer, it's unclear whether it will lead to significant use of Selzentry as part of first line treatment. For one thing, it still requires the Trofile test, which is expensive and time consuming. It is also a relatively new drug, without the long safety record of drugs like Sustiva and Kaletra that are widely used as part of first line therapy. However, like the results from the STARTMRK study (www.projectinform.org/news/08_icaac/102608b.shtml), these results should open up wider use of Selzentry earlier in HIV disease.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

Study may point way forward for bevirimat

A study may help point the way forward for development of Panacos' experimental maturation inhibitor, bevirimat. The study, presented by Dr. Jay Lalazari, found that genetic variations in HIV might be a good predictor of success using bevirimat.

Bevirimat is the first maturation inhibitor to be developed. It works near the same site as protease inhibitors, but rather than blocking the protease enzyme it attaches to its protein target or *substrate*, specifically a site called *Capsid-Sp1*.

Development of bevirimat has been hampered by two issues. The first was formulation problems. The first formulation used in studies was a liquid, which worked well but was thought to be undesirable for commercial development. The first tablet formulation failed to provide adequate drug levels, forcing Panacos to revert to the liquid formulation for the phase 2 studies. Panacos reports having successfully developed a new tablet formulation that it will use for further development.

The other challenge has been a high degree of patient-to-patient variability in responses. Some people experienced very good reductions in HIV levels, while others had very little. These differences were not explained by drug levels or typical drug resistance — leaving the future of the drug in doubt.

This study sought to explain this variability by looking at small changes in an HIV protein called Gag. It specifically looked at whether changes in any of three positions — 369, 370 and 371 — might reduce bevirimat's activity. While there was an average drop in HIV levels of around 1 log, the reductions were much lower for people whose HIV had any of those three changes — called *polymorphisms*. The company looked at the Los Alamos HIV database and found that over 60% of people with HIV were free of such polymorphisms. The 369 polymorphism seems to cause the most profound reduction in bevirimat's activity, followed by 370 and 371.

When people with those polymorphisms were removed from the analysis, bevirimat seemed to result in an average reduction in viral load of around 1.18 logs. This is fairly good but not spectacular.

The future of bevirimat is clouded by uncertainty around Panacos' ability to raise enough money to conduct larger trials. To show the value of this drug, Panacos will need to do such trials. Perhaps this study will point the way forward, focusing future study on people who are free of these three polymorphisms. It remains to be seen whether this will be enough to rescue this somewhat troubled drug. It should be pointed out that while questions remain, it seems well tolerated with no clear signal of any safety concerns.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

RDEA study supports development of new NNRTI

A study supports the further development for RDEA806, an experimental NNRTI from Ardea Biosciences. Results from a phase 2a, 8-day monotherapy dose finding study were presented. Several doses, in both capsule and enteric-coated tablet formulations, were tested for absorption, drug interactions and anti-HIV activity.

Overall, people taking RDEA806 experienced drops in HIV levels of around 1.7log. The responses were better at higher doses. The company has decided to proceed with testing 600, 800 and 1000mg enteric-coated tablets in its phase 2b studies, set to begin by the end of 2008.

There were no interactions between RDEA806 and either Viread (tenofovir) or Emtriva (emtricitabine). It does not interact with the CYP3A4 enzyme pathway, so it does not require Norvir boosting.

There were no moderate to severe (grade 3/4) adverse events reported in the study. No drug related rashes were reported, although the study might not have been long enough to detect such a problem.

After years of little development, the NNRTI class — which includes Sustiva (efavirenz), Viramune (nevirapine) and Intelence (etravirine) — is finally seeing some new drug development. In addition to RDEA806, rilpivarin (TMC-278) and Idexa's IDX899 show promise. Widely considered more tolerable than protease inhibitors, NNRTIs have long been hampered by a high degree of cross-resistance leading most people to have only one shot at this class. All of these new drugs seem to overcome resistance to the first generation NNRTIs, giving many a second chance to take them.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

Better results from vicriviroc with new Trofile test

A study found the second generation Trofile test is better at predicting the success of Schering-Plough's experimental CCR5 drug, vicriviroc. The study was a re-analysis of the ACTC 5211 study, which compared vicriviroc to placebo, each taken with *optimized background therapy* (OBT) in people with experience taking HIV treatments. The original study used the first generation Trofile test, done by Monogram Biosciences, to assess whether the volunteers' HIV used only CCR5 (R5) to enter cells, or if it could use another co-receptor called CXCR4 (X4).

Other research has shown this enhanced Trofile test — also from Monogram — can detect smaller amounts of X4 HIV. The researchers wanted to see if it would better predict whether a person was likely to experience benefit from taking vicriviroc compared to the first generation test.

Overall, the enhanced test found 25 more cases of X4 HIV, out of 114 samples that had originally tested R5 only. Of those 25, 15 had been randomized to take vicriviroc, with 12 experiencing early treatment failure. This suggests that the new test is indeed more accurate at predicting whether people are likely to benefit from vicriviroc, and probably any other R5 drug, like Selzentry (maraviroc).

An audience member pointed out an important potential weakness of this analysis. The researchers did not assess what, if any, affect the other drugs used in the study had in the proportion of people with undetectable HIV. It could be that most of the added benefit thought to be from the more sensitive test was really from other drugs being used in the OBT.

While this new test is better able to detect small amounts of X4 HIV, some HIV doctors and researchers are not altogether convinced that this is a good thing. One Selzentry study found higher CD4 counts in people with X4 HIV despite no reductions in HIV levels. Most doctors and some insurers are requiring the Trofile test to show R5-only HIV in order for Selzentry to be used. Some fear that this new, more sensitive test will further restrict use of this new class of drugs from people who could theoretically benefit from it.

It's important to emphasize that benefit from a R5 drug even without reducing HIV levels is theoretical. While it was seen in one study, there are several potential reasons for the finding. It's important to note the study had a small number of people, and it has not been reproduced by others.

For now, this study only shows that the enhanced Trofile test is better at predicting benefit from vicriviroc, and presumably Selzentry. Use of this more sensitive test in the further development of vicriviroc — and other R5 drugs — may lead to better treatment outcomes for study volunteers.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

Long-term safety study of vicriviroc presented

A study found long-term use of vicriviroc to be safe and effective. The poster was an analysis of an open-label rollover study of just over 200 people who had taken vicriviroc in one of two studies, and found little illness, few side effects, and sustained suppression of HIV for an average of 96 weeks. This study supports the further development of vicriviroc, an experimental CCR5 inhibitor being developed by Schering-Plough.

All participants had taken vicriviroc for 48 weeks in either the VICTOR-E1 or ACTG 5211 studies. People were offered open label, 30mg vicriviroc once a day along with other HIV drugs and then followed for up to 216 weeks. 84% of participants were male and 73% were white. Almost half had a history of an AIDS-defining illness. Average CD4 count was around 200 when people started taking vicriviroc for the first time.

A total of 196 of the 205 people who initially enrolled took vicriviroc for at least 12 weeks, with over 100 completing at least 96 weeks. At 96 weeks, the average drop in HIV levels was around 2 logs, while CD4 counts went up an average of 140 cells. A total of 11 AIDS-defining illnesses occurred in the study along with 15 cancer diagnoses. These are both low rates, considering the advanced HIV disease of the participants when they started vicriviroc. There were also low rates of lab abnormalities.

This study is important as it suggests that long-term use of vicriviroc, and possibly other CCR5 drugs like Selzentry (maraviroc), is safe. As CCR5 drugs have been developed, many are concerned about their safety. Thus far, these fears have not been borne out by either clinical studies or real world use, although the number of people who have taken them is relatively small.

Vicriviroc is currently being examined in several studies, including a large phase 3 study in people with experience taking HIV drugs and an interesting head-to-head study vs. Truvada (tenofovir + emtricitabine/FTC) when either is combined with Reyataz (atazanavir) boosted with Norvir (ritonavir). For information on these and other HIV clinical studies, see www.clinicaltrials.gov.

NEWS ON OPPORTUNISTIC INFECTIONS

Peculiar type of KS emerges in healthier individuals

In a poster presentation, a recent study described a peculiar type of Kaposi's Sarcoma (KS) beginning to emerge in healthy people with HIV. These individuals report higher CD4 counts (>300) and lower (<300) or undetectable viral loads, and yet show signs of this herpes-related cancer. The poster detailed the conditions under which this has been seen in health care settings. It confirms the reports from other cohorts of patients with similar signs of KS disease.

Early in the epidemic, KS was one of the most common symptoms of HIV disease with its characteristic signs of purple lesions on the skin. It posed a serious health threat to those living with HIV, and quickly became an AIDS-defining condition in the 1980s.

Typically appearing as red, purplish, brown or black bumps or blotches on the legs, face and genitals, KS can also spread internally through the stomach, intestines and respiratory system. Before HAART, a case of KS signaled a weak immune system, often with CD4 counts <150 and HIV levels >10,000. Although KS often is not painful, advanced disease can produce swelling and pain.

Over the past decade, HAART has improved the health and lives of people with AIDS, often keeping many of the more serious infections from becoming life-threatening situations. This includes KS, and its incidence has greatly decreased since 1996.

This retrospective study (11/04 to 07/08) conducted by the University of California San Francisco culled data on 10 gay men with signs of KS despite having healthy immune systems. CD4 counts averaged above 300 and viral loads <300. The average age was 59, time living with HIV was 17 years, and time living with KS was 2.5 years. KS biopsies were prospectively performed.

Of the 10, 9 had at least one KS lesion on their lower limbs, and 7 only had lesions there. One had a lymph node involved while 3 had mild swelling. Two reported pain from lesions on their feet. None had internal KS, and none have developed it since. Nine were on HAART when diagnosed with KS, and all are currently on HAART.

Among those who did not have their KS treated, the disease has remained fairly stable. Of those who did, it included surgical removal, radiotherapy, topical alitretinoin, intralesional vinblastine, or liposomal doxorubicin. All of these treatments have shown mild to moderate improvement in symptoms. None have faced eruptive KS or organ disease or have had other OIs.

Although the study's purpose was to collect the clinical symptoms and markers of this type of KS disease, the poster went so far to state that: "it is our recommendation that they should be managed conservatively". It stated that a person's adherence to HAART could be revisited to improve its effectiveness in controlling the KS. Also, it appears that protease inhibitors do not offer any more benefit over NNRTIs in treating this type of KS.

Prior to the AIDS epidemic two types of KS were seen. The first type affected older men, usually from the Mediterranean region. This form was slow, non-aggressive and rarely led to serious health complications. The second affected mostly young African boys and was typically aggressive — spreading and causing disease rapidly.

Unlike the KS seen among people with HIV in the 1980s, these men show symptoms that persist yet are not aggressive, invasive or lethal. This type of KS appears more like the type affecting older Mediterranean men. Taken together with the data from other recent cohorts (Chan *et al*, Nasti *et al*, Martinez *et al*, and Krown *et al*), this study's observations perhaps show a changing landscape in KS disease. This may well call into question other emerging issues of aging with HIV disease.

NEWS ON OPPORTUNISTIC INFECTIONS

MRSA infections gaining ground in people with HIV

Several presentations revealed a mounting concern over the relationship between HIV and MRSA, or *methicillin-resistant Staphylococcus aureus*. Although the studies looked at different aspects of this infection, the data underscores at least a 300% increase in the number of MRSA infections over the past few years. Although not fully understood, HIV is believed to be a risk factor for MRSA.

MRSA is an antibiotic-resistant form of *Staph*, a common bacterium. MRSA infections of the skin and soft tissue are fairly treatable though are growing more stubborn. The most common strain in the US is USA 300, along with USA 400, 500 and others. The good news from one study is that taking effective HAART during the past year lowers the risk of infection. Washing hands often and not touching the face also reduces the risk.

MRSA normally occurs in health care settings where it is called HA-MRSA, or *hospital-acquired MRSA*. Yet, a rising number of *community-acquired infections* (CA-MRSA) have appeared in gyms, jails, shelters, barracks and other places with close personal spaces. Its resistance to a large family of antibiotics makes treating the infection difficult, especially for people with HIV who may take drugs that interact with the antibiotics.

One study done in Chicago showed an astonishing rate of 952/100,000 cases of MRSA in HIV-positive people vs. 156/100,000 cases in others. As well, the rate greatly increased from 373/100,000 cases in 2000–03 to 1,426/100,000 cases during 2004–07 — an almost 4-times higher rate.

A second study in Chicago showed a similar increase between these periods, from 190/100,000 cases to 779/100,000 cases in HIV-positive people — a 4.1-times higher risk. The Veterans Aging Cohort Study (VACS) found a nearly 3-times higher rate of MRSA among HIV-positive people (122 of 2,652) vs. HIV-negative people (43 of 2,728) over 7 years of study.

A retrospective South Carolina study found a 3-times higher risk for MRSA in people who had used antibiotics within the past year and a 2-times higher risk for those with a lowest ever (*nadir*) CD4 count below 200. Unlike other studies, preventive Bactrim (TMP/SMX) therapy did not protect against MRSA. And, according to the VACS, MRSA recurs more often in HIV-positive people.

However, taking HAART for at least the past year greatly reduced the risk for MRSA, with no differences on type of HAART used. Data also suggest that HIV-positive people respond about as well as HIV-negative people to the antibiotics used to treat MRSA. Rifadin (rifampin) and Bactrim appear to be the most effective, yet they can pose difficulties. Rifadin can cause severe interactions with some HIV drugs while Bactrim can cause allergic reactions for many.

The emerging intersection of HIV with MRSA can further complicate our current response to treating both diseases. Further study needs to uncover additional information on who is at risk and how best to manage these infections. Until then, the best prevention to MRSA is properly adhering to a HAART regimen and maintaining good personal hygiene, along with regular monitoring and reporting of skin and soft tissue infections.

NEWS ON HIV RELATED CONDITIONS

Surprising rate of serious heart condition found in those on HAART

A poster presentation revealed a high rate of a serious heart condition called *pulmonary arterial hypertension*, or PH, in people with HIV. The condition is high blood pressure in the pulmonary artery, the main artery leading from the heart to the lungs.

PH is not readily diagnosed due its lack of symptoms and often emerges later in HIV disease as a more life-threatening condition. It is more common in people with HIV, even more so for those with symptomatic diseases, reaching a rate of about 1 in every 200 people with AIDS (pre-HAART era).

This retrospective study sought to find the rate of PH separate from several known risk factors. HIV is an independent risk factor for PH while injection drug use (IDU), excessive alcohol use and smoking also increase its risk. The study evaluated the rate of *pulmonary artery systolic dysfunction*, which is abnormal peak pressure in the pulmonary artery. People whose HIV disease was well controlled on HAART were divided into two groups: those with and those without PH.

The study, conducted at the National Naval Medical Center, included 91 people who averaged 37 years in age, CD4 counts of 583, nearly 11 years living with HIV, and 5.4 years on HAART. These factors did not vary much between the two groups. Viral loads were also similar between them. Extensive medical histories were taken to exclude risks of heart disease, including genetic factors and lifestyle issues such as smoking and IDU.

The results showed a 5.5% rate of PH in this cohort (5 men total, 2 black and 3 white), which is a high rate compared to similar studies of PH. However, there were no clinical markers that were associated with this rate. In those with PH, the condition was mild and without symptoms. CD4 counts and viral loads did not affect the risk. Other risk factors also did not relate to PH such as cardiac risk factors, lowest-ever CD4 count, use of protease inhibitors, or high risk for AIDS.

Three of the five with PH also had a *diastolic* dysfunction, though this was statistically not significant. Although other studies show that HAART lowers the risk of PH, this cohort could not draw that conclusion. More prospective study needs to determine whether HIV-positive people on potent therapy with mild PH will eventually develop symptomatic PH. For more information on this condition, read Project Inform's publication, *Pulmonary Hypertension and HIV*.

NEWS ON HIV RELATED CONDITIONS

Risk of a hospital stay high after starting HAART

A poster showed a high rate of hospitalizations within the first three months following the start HIV therapy (HAART). Further, the rate of hospital stays within the first 45 days of being on HAART for those who responded well to therapy were surprisingly comparable to those who didn't respond well.

Although taking HAART reduces HIV-related illnesses over time, the study sought to find the rate of hospital stays within the first year after starting therapy. People who start HIV therapy are at risk for a variety of illnesses. These include adverse drug reactions, opportunistic infections, and *immune reconstitution inflammatory syndrome*, or IRIS (www.projectinform.org/info/iris/index.shtml).

In this retrospective study (1997–2005) by the John Hopkins HIV Clinical Cohort, data on the hospital stays of 1,329 people were collected and examined. The study included from 6 months before starting HAART up to a year afterwards.

Two groups were followed based upon their ability to reach a 1 log (90%) reduction in their viral loads within six months. Responders (965) were those who achieved the 1 log decrease, and non-responders (362) were those who didn't. Women comprised about 35% of the individuals, while nearly 4 in 5 were Black and nearly 1 in 5 was White in this cohort. More than 2 in 5 were injection drug users (IDUs).

The results show a high rate of hospital stays for both groups within the first 45 days after starting HAART — just above 80 stays per 100 person-years on average. For responders, their hospital stays fell significantly between 45 and 90 days while non-responders showed no significant change over one year of follow-up. Also, both 45-day rates were comparable to the rates seen before starting HAART for each group.

Risk factors for hospitalization after starting HAART included lower CD4 count (<100), being female and IDU. Other factors did not contribute to these rates, which include age, type of HIV drugs used, and various time periods during the study.

Several factors may limit this study's findings. First, it included a high number of injection drug users, which is significant for that community but may not translate well to the general population. Second, the study was conducted at a single health care center, which may limit how it applies to demographic differences seen in parts of the US.

From these data, keeping a close eye for symptoms of illness during the first 3 months on HAART appears to be in order for both health provider and patient to help prevent possible hospital stays. Prospective studies that look at the reasons for these stays could provide more specific information on the types of clinical and lifestyle factors that better predict an individual's risk for a hospital stay.

COMMENTARY ON CURE BASED RESEARCH

Zinc finger technology takes a step forward

A poster presentation described results from a recent study using zinc fingers as a possible anti-HIV therapy. Though this approach has not reached human study, these results show some promise by creating lines of CD4 cells that have become permanently resistant to HIV infection. This occurred in lab cultures as well as in mice.

Zinc fingers are a family of proteins that can alter specific genes in a person's DNA. In this study they were used to change, or mutate, CCR5 (R5) receptors from allowing HIV to enter CD4s. R5 is the more common co-receptor that HIV uses to enter these cells.

A small number of HIV-positive people who naturally resist HIV infection have the *R5 delta32 mutation*. Those who get this mutation from both parents are generally quite resistant to HIV infection. Those who get it from one parent tend to experience slower progression of HIV disease.

In this study, researchers used a technology to create *zinc finger nucleases (R5-ZFNs)* to bind to the area of DNA that codes for R5 receptors. In theory, this DNA change would mimic the delta32 mutation explained above. After a one-time exposure to the R5-ZFNs, the mutation would take place; and as those CD4s divide and multiply, the mutation would carry into the new CD4s.

Results showed that more than half the targeted CD4s were affected by the R5-ZFNs. After the mutation in these cells occurred, the CD4s showed resistance to R5 HIV. Then, as these modified CD4s continued to divide over several weeks, the mutations carried over to the new CD4s which also remained resistant to R5 HIV.

Further, these new CD4s multiplied in special mice that lack normal immune systems. The modified CD4s increased more than 2- to 3-times higher in mice with HIV. Beyond that, after 50 days of HIV infection and treatment with R5-ZFNs, the mice showed a 7-fold decrease in viral load compared to mice without modified CD4s.

The ZFN-treated CD4 cells seem to be permanently changed to prevent R5 HIV infection in those CD4s. Also, the modified CD4s and their offspring seemed to function normally beyond resisting R5 HIV. An additional benefit to treating CD4s with ZFN was an increase in CD4 counts, which may better suppress HIV replication.

The hope that this approach offers sounds extraordinarily promising. However, as bright as these data appear, there are still hurdles to overcome. Since this study evaluated its proof of concept with portions lasting several weeks, the long-term effects of genetically altered R5 remain unknown, especially having not been studied in humans. We simply don't know how these R5-ZFNs could affect or change HIV or even how they could affect a person's immune system over time.

News briefs from ICAAC / IDSA ...

For complete coverage on these topics, go to www.projectinform.org/news/08_icaac/index.shtml.

New blood test may facilitate better TB diagnoses

Diagnosing TB (*Mycobacterium tuberculosis*) infection, active and latent disease, and treatment success can be difficult. In fact, accurately finding active TB disease in people with HIV is complicated by poor results from commonly used tests in this population, such as the tuberculin skin test (TST) and acid fast bacillus (AFB) smear. A poster presented early data on a small study examining a new blood test called TSPOT to more accurately diagnose active TB in HIV-positive people. The results showed generally positive data on the test's ability to find TB in 8 of 10 of the people with active TB. It generally outperformed TSTs and AFBs. Though more research is needed to more fully qualify its effectiveness, it may lead to being a better diagnostic tool for testing and treating TB in HIV-positive people.

Risk factors for anal cancer include low CD4 count

A poster presented data from a small retrospective study on the risk factors for anal cancer in HIV-positive men. Infection with the human papillomavirus (HPV) is a growing health concern for people living with HIV, especially men who have sex with men. For each case that was diagnosed (15 total), three HIV-positive men without anal cancer were randomly chosen as a control group. CD4s for the group with anal cancer averaged 224 while the other group averaged 409. As with most co-infections in HIV disease, HIV-infected men appear to be more at risk for anal cancer as their CD4s decrease towards 200 and below. Also, higher viral loads and longer time living with HIV were not shown to be risks for anal cancer. These results add to the growing body of information regarding HPV disease in people with HIV. Though no great leaps have been illuminated with these results, they continue to point to heightened screening and diagnosis of HPV disease in all people living with HIV.

Syphilis does not increase risk of AIDS or death

A poster presented information on the effect of syphilis on an HIV-positive individual's risk to AIDS and/or death. This common sexually transmitted infection can decrease CD4 counts in people with HIV. Syphilis can also increase HIV levels, which can stay elevated even after its successful treatment. Results from a prospective, observational study was conducted using a US military cohort of 2,239 people. The study analyzed time to AIDS or death or time to death alone. It adjusted for CD4 count, age, race, gender and hepatitis B/C status. The results showed that having a confirmed or probable case of syphilis was not a risk factor for progressing faster to an AIDS diagnosis or death.

Adding GM-CSF to hepatitis B vaccine fails to work

People living with HIV are at risk for getting the hepatitis B virus (HBV). They also have a higher risk of HBV disease and death. Although current HBV vaccines protect about 90% of the time, they don't offer the same level of protection for HIV-positive people. To be most effective, the vaccine should be given at higher CD4 counts. Yet even this does not ensure immunity and not all people with HIV have high CD4 counts at the time of vaccination. A poster presented phase II data on an HBV vaccine given with GM-CSF (*granulocyte-macrophage colony-stimulating factor*), a protein produced by many immune cells. This was done in the hopes for a more durable protective effect from the vaccine. Unfortunately, the results showed that using GM-CSF did not produce any added protection over the group given the placebo. Studies like this one, even with disappointing results, are critical to finding ways to further protect people living with HIV at risk for HBV infection.

Meningococcal vaccine appears safe in youth with HIV

A poster showed positive results from a study of the meningococcal vaccine (MCV4, Menactra) in youth living with HIV. The vaccine prevents infection with the *N. meningitidis* bacteria that causes several meningococcal diseases such as meningitis. The safety of the vaccine has not been studied in HIV-positive adolescents. This phase I/II study followed 3 groups of 319 youth aged 11 to 24 years. All three groups took one dose of the vaccine at study start. At 24 weeks, group 1 received a second dose while groups 2 and 3 were randomized to take or not take a second dose. The results showed that the vaccine was safe to use as two doses in HIV-positive youth aged 11 to 25 years of age. This was true across the spectrum of CD4 percentages studied.

Study suggests a more virulent HIV today

A poster presented interesting information on HIV's possibly maturing "virulence". This ongoing Tri-Service AIDS Clinical Consortium study highlights a gradually lowering trend in baseline CD4 counts in newly diagnosed people in today's epidemic compared to 1985. The retrospective study looked at 1,944 newly diagnosed people at 7 US military medical centers. Each had their first CD4 count done within 6 months of diagnosis, and no one took HIV therapy before their baseline CD4. A lowering trend in average CD4 counts were noted over a series of four periods of 6, 5, 6 and 3 years at 632, 555, 495 and 499 CD4s. Although the study suggests these lower CD4 counts may be due to a more "virulent" HIV today, a 2004 Swiss study contradicts this with a result that HIV is not more virulent today. Also, very few in the study were women, much less than what is seen in the US epidemic. As well, this was a military cohort and no information was provided on factors such as rates of deployment or co-morbidities — each of which could skew the results.

Four weeks of therapy enough to prevent mother-to-child transmissions

A poster of an Irish study shows the US guidelines for HIV-exposed infants getting 6 weeks of HIV therapy to prevent mother-to-child transmission (MTCT) can be shortened to 4. The study mentions the US Guidelines' lack of definitive evidence supporting its recommendation. This retrospective audit of the Irish Prevent MTCT program examined the pregnancies of 868 women from 01/99 to 12/07. One of two regimens were given to the infants: Retrovir or Retrovir + Viamune + Epivir. The results showed that the MTCT rate equaled 1%, which is lower than global standards of an acceptable MTCT rate. These results likely won't be enough to encourage the US to change its Guidelines, but they may persuade prospective study of this issue.

ADAPs and maximizing health outcomes for all eligibles

The federal AIDS Drug Assistance Program (ADAP) is set up in each state to ensure that those living with HIV who cannot cover the cost of their HIV meds can still access them. Due to tightening state budgets, ADAPs are providing services to an ever-growing list of people in need, often limiting eligibility on a first-come, first-served basis. This has caused some who may more quickly progress in their HIV disease to not start HIV therapy soon enough. A poster presented data from a study that used a simulated model with characteristics from the Massachusetts ADAP and prioritized enrollees by CD4 count when the ADAP is faced with limited resources in the hopes of minimizing the rate of adverse health events while containing costs. The model revealed that basing eligibility on CD4 count rather than on a first-come, first-served basis resulted in lower rates of opportunistic infections and death while not negatively impacting others with better health who had to wait. This model only simulated an ADAP, and it's unknown how this information would be used by US ADAPs. However, it does lay some interesting groundwork for looking at this issue of maximizing limited state resources.

About the joint ICAAC / IDSA meeting:

ICAAC and IDSA held a joint meeting this year. ICAAC is one of the most important AIDS conferences that Project Inform attends and collects information from annually. ICAAC presents recent data from completed and ongoing studies on a range of topics, including HIV. Research data are presented in many ways at the conference and are described below.

PROSPECTIVE STUDIES: These are designed to answer certain questions, like those about drug safety and effectiveness or symptoms and rates of various opportunistic infections, among others. The data from these studies generally provide the strongest observational data since they were designed to answer specific questions. They can be of any size.

RETROSPECTIVE STUDIES: Here, researchers extract data from already completed studies to answer other questions that could be addressed by using those data. These studies tend to have less power in their observations since the data may be skewed by confounding factors that are unknown or unaccounted for. However, important results can still be found through them and often lead researchers to consider studies on similar topics.

ABSTRACTS: These are brief synopses of data from studies of all sizes. They generally present short, concise data in four parts: background, methods, results and conclusions. Nearly all abstracts are available on the conference website. These study “snapshots” can often be too brief to provide truly meaningful data to the public.

POSTERS: These are presented daily in an auditorium and provide more in-depth data than an abstract. Study presenters are often present to answer questions from conference attendees. Some posters are available on the conference website. Posters usually provide meaningful data.

BREAKOUT SESSIONS: These can be small or large in size and often get presented in rooms throughout the conference center. Most of the time, up to 6 or 7 researchers will present data from their studies, all of which have a common theme that’s reflected in the breakout session title. These may or may not be accompanied by abstracts and/or posters.

SLIDE PRESENTATIONS: These occur in rooms or auditoriums, depending upon the nature of the information. Slide data are often not available online, and they may or may not be accompanied by a poster or abstract.

PLENARY SESSIONS: These normally open the full conference or occur each day of the conference and will highlight topics with high community interest. Some are recorded and available on the conference website.

LATE-BREAKERS: These normally occur at the end of a conference or at the end of each day. They also highlight topics with high community interest, though less may be known about the presentations’ contents beforehand. Some are recorded and available on the conference website.