End Stage Liver Disease Emerges As Leading Cause of Death in PWAs with Hepatitis C

‘Big problem on our hands’

“While many people with HIV are living longer, more productive lives,” Michael Marco explains, “a good many who are also co-infected with the hepatitis C virus are winding up in the hospital and dying of end-stage liver disease. As an activist who eschews hepatitis C media hype (e.g., New York magazine’s outrageous 2000 cover story, “Hepatitis C, The Silent Killer”) and alarmist co-infection data from misleading, outdated and small retrospective case studies, I am here to say that we have a big problem on our hands.”

End stage liver disease (ESLD) (characterized as conditions, including encephalopathy, ascites, jaundice, gastrointestinal bleeding, hepatorenal syndrome or peritonitis) in PWAs with HCV appears to be a leading cause of hospital admissions and death according to a number of U.S. and European data presentations at the 8th Conference on Retroviruses and Opportunistic Infections. Conflicting data from the conference (and recent journal articles) have also reinvigorated the old debate of whether HCV infection independently leads to accelerated disease progression and death in PWAs.

End stage liver disease as the leading cause of death in HIV clinical - continued on page 5 -

Highly active antiretroviral therapy (HAART) should be offered to every HIV-infected individual with a(n):

<table>
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<tr>
<th>Previous HHS Guidelines</th>
<th>New HHS Guidelines</th>
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<td>CD4 &lt;500/mm³ or HIV &gt;20,000/mL</td>
<td>CD4 &lt;350/mm³ or HIV&gt;55,000/mL</td>
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Abducción de la Inducción
La Aprobación Federal De la Droga CMV Oral
Rendiría la Terapia Inicial de Retinitis CMV Más Facil

‘Doce años en la venida’

En el 27 de febrero el Comité Consultor Antiviral Endroga del FDA reunió para considerar una aplicación para la aprobación de valganciclovir de Hoffmann-La Roche para el tratamiento de retinitis de CMV en la gente con SIDA. Michael Marco preparó este papel de la posición a favor de TAG. Una decisión en la aplicación se espera luego este mes.

Retinitis de cytomegalovirus (CMV), un afectar de la enfermedad de viral la pérdida de ojos y causa de la visión, era una vez una enfermedad rara que ocurre sólo entre individuos con síndromes primario de inmunodeficiencia o desórdenes de autoinmune, recipientes de trasplante de

- continued on next page -
the organizers of the Conference appeared especially eager to highlight the significant modifications that appeared in the February 2001 update of the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults & Adolescents.

Prior to the conference I heard a rumor that the organizers had turned down a request by guidelines panel co-chairs Anthony S. Fauci (NIAID) and John Bartlett (Johns Hopkins University) for a press conference to announce the new guidelines. So, at the opening press session I questioned Retrovirus chair Connie Benson of the University of Colorado whether they had indeed turned down a request by Drs. Fauci and Bartlett. “No at all,” said Dr Benson, who is also a co-chair of the government’s top HIV clinical research program (the AACTG). It turns out the only request she heard had come from a NIAID press person. “Do you think I would actually turn down Dr. Fauci?” she asked. And in fact, as the conference opened, the only document NIAID had shown the conference organizers was an anemic two-page press release; the Retrovirus press person had to download a copy of the new guidelines from the internet.

Why the low-key reception? Well, just as enthusiasm for the early use of AZT was deflated by the release of the Concorde study results in 1993, so the 2001 treatment guidelines finally depose the ailing “Hit early, hit hard” orthodoxy.

Just as the enthusiasm for the early use of AZT was deflated by Concorde in 1993, so the 2001 treatment guidelines finally depose the ailing “Hit early, hit hard” orthodoxy.

Over 5,000-10,000 HIV RNA copies/mL wasn’t such a great idea after all,” the guidelines panel co-chairs and the Retrovirus organizers all felt it was more opportune—or more expedient—to skate over the matter as casually as possible, as though the new guidelines represented a simple and relatively uncontroversial recalibration of the standard of care.

An honest mistake?

Of course, TAG has been covering this controversy for a long time. When Mark Schoofs from The Wall Street Journal called me, he said, “This is a good thing. People don’t have to go on therapy so early.”

“Well, yes,” I said, “but it would have been much better to have a clear answer from a randomized, controlled trial by now.”

“Well, Tony Fauci says that’s unfeasible.”

“Well, if he says so, it must be true,” I replied, “but if they’d started one in 1996, we might have an answer by now.”

“You sound angry.”

“I am angry. Thousands of people were put on therapy too early, and some of them developed life-threatening side effects, or resistance, and they would have been fine if they had just waited.”

Was not seeking evidence for such a sweeping policy simply an honest mis-

The death of the eradication hypothesis?

The NIH press release distributed at the conference quoted Dr. Fauci as saying, “We know that we cannot eradicate HIV infection with currently available medications.” But we have known that HAART cannot eradicate HIV ever since the discovery at the laboratories of Bob Siliciano, Doug Richman, and Tony Fauci in 1997 of latent HIV reservoirs in resting, provirally-integrated CD4 cells. The original HHS guidelines came out that same year. So the “Hit early” approach could not have been based solely—or even mainly—on the feasibility of eradication.

Treat HIV like any other infectious disease?

In the minds of some, the “Hit early” approach was based on the idea that, in Bruce Walker’s words, we should “treat HIV-1 like any other infection—treat it.” Well, sure. The question is, when?

HIV-1 is not like other infections. Some, such as bacterial infections, can be cured with antibiotics. Obviously, if HIV could be cured, we would try to cure people. Persistent viral infections, such as herpes, cannot be cured, and we do not treat them chronically; instead, we only treat them when outbreaks occur. HIV is like neither bacterial infections nor herpes. It cannot be cured. It is
Mary Jean Slugs It Out in Gaithersburg: Roche’s Valganciclovir is Recommended for Approval

On 27 February at the sad and lonely Gaithersburg Holiday Inn, the FDA’s Antiviral Drug Advisory Committee (ADAC) held a hearing to discuss Hoffmann-La Roche’s NDA for valganciclovir for the treatment of CMV retinitis in people with AIDS. One would have thought that CMV - once the second leading cause of death in PWAs - was an infection on par with toe fungus by the meager audience turnout. It was, however, an historic day for CMV research: the first oral drug with real efficacy to treat CMV was about to be recommended for approved. One couldn’t help but wonder, “Where was this drug ten years ago when we really needed it?” The ADAC committee was absent of some of its members, most notably Roy “Trip” Gulick, the acting-chair. Roger Pomerantz filled in nicely for Trip, and luckily old-time HIV experts Princy Kumar (Georgetown) and Chris Mathews (UCSD) were present for a reality check. The advisory committee was infused with some well-respected ophthalmologists who unfortunately got “stuck-on-stupid” during the question and answer period. Roche’s Mary Jean Stempien, who is considered the mother of IV ganciclovir from the late 1980s, was back at the helm presenting the valganciclovir safety and efficacy data. Emory’s Dan Martin, the consummate over-accurer and good-natured ophthalmologist, was on-hand to answer the technical ophthalmologic questions.

I had wondered why the FDA’s Antiviral Drug Products Division requested a public hearing on valganciclovir, the valine-ester prodrug of IV ganciclovir. The valganciclovir data are excellent and there are years of experience treating thousands of people with IV ganciclovir. A source close to the Division told me the hearing was needed because: 1) only one trial of 160 people was being used for efficacy analysis; and 2) the sponsor was requesting an indication for CMV induction and maintenance therapy but only had efficacy data from the 4-week randomized valganciclovir vs. IV ganciclovir induction phase. Roche pointed out three reasons it deserved an indication for maintenance therapy:

1. Valganciclovir provides systemic exposure (AUC) comparable to IV ganciclovir;
2. Valganciclovir’s efficacy in the induction phase—the most rigorous test of a CMV drug—was similar to IV ganciclovir;
3. Valganciclovir offers exposure 10-times that of oral ganciclovir (and it’s approved for maintenance), valganciclovir should be considered at least as effective for maintenance.

Mary Jean Stempien and Dan Martin were on their toes the entire day answering questions and showing a myriad of back-up slides. Some of the pharmacology questions were interesting (i.e., “Is using AUC the best gauge for determining bio-equivalence”), but most of the others were too painful to sit through. I wondered if some of the ophthalmologists really knew HIV clinical care and understood the entire HIV-positive individual, not just his or her eyes. One ophthalmologist did not like the rate of anemia attributed to valganciclovir during the open-label maintenance phase. He repeatedly wanted to know if Roche would consider lowering the maintenance dose. Mary Jean began answering his questions simply and calmly, but when he just wouldn’t let up, she lost her polite and professional tone of voice and let him have it. I have paraphrased her comments below.

Since the ADAC already had a straightforward TAG statement that recommended valganciclovir for approval, I decided to discuss the questions which were soon to be voted on. With regard to its efficacy, I said that valganciclovir was comparable to ganciclovir, and it’s surprising that even one study was ever completed during the HAART era. I reminded them that after 20 years of AIDS, an effective oral CMV treatment is still not available. I also reminded them that Roche headquarters in Basel wanted to stop the development of valganciclovir because of fear that CMV had gone away and there would be no market. As for its safety, I said valganciclovir is IV ganciclovir in a pill and all good HIV doctors know how to manage ganciclovir’s hematological toxicities. When it came to the question of valganciclovir’s effectiveness as maintenance, I informed the ADAC that most CMV drugs were approved for induction and maintenance therapy using an immediate versus deferred trial design. Such studies only told us that the drug was better than nothing (deferring) and were stopped so early by a DSMB that no real maintenance data exist. Why was the bar being suddenly raised for valganciclovir?

In the NIH press release, Fauci went on to say that the revised guidelines present “evidence-based recommendations for initiating antiretroviral therapy that take into account both the benefits and potential risks.” But the guidelines themselves admit that, “The optimal time to initiate antiretroviral therapy is not known.”

The “evidence” to which Dr. Fauci referred is a random grab-bag of observational studies which are contradictory and hardly definitive. One can conclude whatever one wants to from these observational studies: if you favor early treatment, you can find studies that do too; if you favor later therapy, other studies will back you up.

chronic and persistent. And it never goes into full latency—unlike herpes. Treatment requires complex, expensive, sometimes toxic, combination therapy. Full adherence is difficult if not impossible. The development of drug resistance is a constant threat.

Solid results from evidence-based medicine?
up.

Weaker evidence from observational studies?
Observational studies, despite their limitations, are practically the only “evidence” we have right now about the clinical benefits of various starting thresholds. Several large cohort studies presented at the Retrovirus conference in February 2001—most of them in poster form because they did not fit the preferred weltanschauung of the conference organizers—suggest that, while starting when the CD4 count is below 200 is clearly less effective than starting when it’s above, there is no difference among groups starting with higher CD4 cut-offs. Even very high viral loads may make little difference.

What next?
It would be nice if we could really have treatment guidelines based on evidence from well-controlled studies. But perhaps we missed the chance to initiate such studies because so many were captivated by the euphoria that accompanied the adoption of HAART after 1996. Sometime in 1997, when David Barr and I were in Anthony Fauci’s famous corner office at NIAID, we asked him to support a major clinical trial of when-to-start. “It’s the most important question in HIV therapy,” he agreed. But nothing happened. During the 1998 adult AIDS Clinical Trials Group (AACTG) recompetition, NIAID once again missed the opportunity to encourage—or force—the research community to address the question.

In early 2000, after considerable activist pressure, NIAID’s Division of AIDS appeared to recommend $42 million in funding for a when-to-start trial and held several workshops to discuss methodology and feasibility issues. These initiatives were smothered in the cradle by AACTG leadership and community representatives who dismissed the feasibility of long-term research. This round of when-to-start ideas was finally buried at the NIAID Council meeting in January 2001.

Starting therapy when the CD4 count is below 200 is clearly less effective than starting above 200, but there is no difference at higher CD4 cut-offs—even at very high viral loads

As the press started to get hold of the new treatment guidelines, it was natural to ask Dr. Fauci why there were no clinical trials to answer what appeared to be such an important question. Even though the NIAID-sponsored feasibility studies had yet to be completed, Fauci told ABC News, in a story aired on January 31, 2001, that such a study would be, “logistically impossible to do ... No one has yet been able to come up with a protocol.”

Some have suggested doing a when-to-start study in a developing country. But in places that can barely afford HAART or the necessary infrastructure, treating people with CD4 counts over 350—or even over 200 cells/mm3—may be a luxury such countries can ill-afford, even if some so-far-undetected benefit actually accrues to such a strategy.

At the Retrovirus conference, one of the leading figures in the Adult ACTG told me that, having dismissed the idea of a randomized when-to-start study with clinical endpoints, the AACTG is now exploring the feasibility of 1) smaller, randomized when-to-start studies looking at viral load, CD4 counts, and other laboratory parameters, and 2) establishing a larger observational cohort which, supposedly, could shed light on the question.

There are several problems with this approach. The smaller randomized study with surrogate markers simply wouldn’t answer the question of whether people who start treatment earlier live longer or not. Obviously, CD4 counts would be higher, and RNA levels lower, in the group that was treated earlier. But this might not affect longer-term outcomes. A prospective observational study would be expensive, wouldn’t answer the question any sooner than a randomized controlled trial, and would suffer from all the limitations of the observational studies described above.

It appears unlikely that any of the NIH-funded trials networks will do a controlled clinical endpoint study looking at when to start. It appears even less likely that such a study could be carried out in resource-poor developing country settings. Perhaps the Europeans, in conjunction with other developed countries such as Canada or Australia, may do such a study—but clinicians in those countries already tend to start treatment later.

More likely, we’ll have to continue to rely on observational studies with accumulating inferences, hints and clues from smaller randomized studies, as well as new and emerging insights about predictors and correlates of various drug-related adverse events, to guide the standard of care for the next few years. †
cohorts
Epidemiology studies from various HIV cohorts in the U.S. report co-infection in 25-75% of individuals. The higher incidence rates are often found in major metropolitan inner-city clinics treating persons with a history of intravenous drug use. Many HIV clinics in southern Europe have a co-infection exceeding 50%. Co-infected HAART-treated individuals who are living longer and entering their late 40s and 50s are having their HCV disease go from asymptomatic to symptomatic and, worse yet, from symptomatic to ESLD. For 20% of HCV-infected individuals—especially those co-infected with a nadir CD4 cell count of <200 cells/mm^3—progression to ESLD is only a matter of time.

Researchers in Madrid documented a steep rise in the number of hospital admissions and deaths caused by HCV- and HBV-related ESLD between 1995 and 2000. Of the 843 HIV-positive individuals seen at the institution over the five year period, 46% had viral hepatitis; about 30% of whom had HCV. Hospitalization due to ESLD rose from 5.2% in 1996 to 8.4% in 2000. In fact, 43% of all deaths among the HIV-positive individuals were caused by ESLD.

HCV ESLD was again the leading cause of death in a French HIV cohort. French researchers reported that there were 105 deaths recorded between 1998-1999 in their 2,200 person cohort, and HCV ESLD was the cause of 29% of them. Similarly, investigators from northern Italy found that HCV ESLD was the leading cause of death in their HIV-positive individuals in 1998 and 1999.

This surge in deaths due to ESLD in co-infected individuals is not confined to southern Europe. At Cook County Hospital in Chicago where over 50% of the HIV-positive individuals have HCV, researchers there found ESLD to be the cause of death in 35% of the individuals between January 1998 and September 2000. Overall, ESLD was the second leading cause of death after sepsis (38%).

Does HCV infection negatively affect HIV disease?
A number of studies presented at the Retrovirus meeting attempted to answer the controversial co-infection question: Does HCV have a negative impact on HIV disease progression and survival? The best data came from the well-established European HIV cohorts and the Johns Hopkins group.

Studies concluding “Yes”
Researchers from Montreal’s McGill University presented results from a 182 HIV-positive patient retrospective chart review suggesting that HCV co-infection was associated with faster progression to death and increased hospitalization. 78 HIV/HCV co-infected individuals were compared with 104 HIV-mono-infected individuals seen at the McGill clinic between January 1996 and June 1999. While both groups had similar baseline demographics (38 years old; 70% male; 310 CD4 cells/mm^3; HIV RNA of 10,000 copies/mL), 23% of the co-infected individuals were on HAART compared to 35% of those infected with HIV alone.

The rate of opportunistic infections was 9.77 vs. 7.91 per 100 person years; rate of death: 6.67 vs. 2.27/100 person years; and hospitalization rate: 15.03 vs. 6.79/100 person years in co-infected and mono-infected individuals, respectively. Co-infection was therefore associated with a faster progression to death. After adjusting for differences in baseline and follow-up measures of CD4 cell count, HIV viral load, duration of HIV infection, and use of HAART, the relative risk of death for HCV/HIV co-infected individuals was 11.7; the relative risk of hospitalization was 2.5.

Even though HAART use was controlled for, the authors speculated that the differences in HIV clinical progression “may be explained in part by the lower use of HAART.” The data here are important, but it is difficult to garner definitive conclusions from such a small, retrospective single-institution case study.

The McGill study corroborates results of a much larger analysis from the Swiss HIV Cohort—which was recently published in the Lancet. 3,111 individuals initiating HAART between June 1996 and May 1999 were prospectively followed for survival, clinical progression, HIV RNA suppression, CD4 cell recovery, and HAART change according to HCV status. Of the 3,111 HIV individuals who were followed for a median of 28 months, 1,157 (37.2%) were co-infected with HCV. 1,015 (87.7%) with a history of IVDU. There were significant differences in baseline HIV characteristics of the HCV-infected and HCV-uninfected individuals: 27.7% vs. 23.5% had AIDS; 58.9% vs. 52.3% were antiretroviral treatment naive; and median CD4 cell count was 172 vs. 222 cells/mm^3.

After the initiation of HAART, there was no association between HCV infection and the probability of reaching an HIV RNA <400 copies/mL. There were, however, differences with regard to CD4 cell recovery. After one year on HAART, the probability of fail-

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Throughout the follow-up period, 7.5% of the HCV-infected individuals developed an OI compared to 4.7% of the HCV-uninfected ones (p=0.001). Death was also more common in the HCV co-infected group: 8.8% vs. 4% (p<0.001). Interestingly, there were significant differences in the probability of clinical progression to AIDS and death when data were stratified by active IVDU and HCV. The estimated probability of clinical progression at 2 years was: 6.6% for HCV-/no active IVDU; 9.7% for HCV+/no active IVDU; and 15% for HCV+/active IVDU.

The Swiss study is one of the first (and largest) to detect an increase in OIs and death due to co-infection with HCV. One explanation for this could be the impaired CD4 cell recovery in HCV-infected individuals on HAART. These results will need to be confirmed in another study of equal size in a different country. (The fact that >85% of these 3,000 Swiss individuals had an HIV RNA <400 copies/mL makes this author think that Switzerland is not "real world" when it comes to HIV and its medical management.)

Impairment of CD4 cell recovery in HIV/HCV co-infected individuals on HAART was also seen in a Spanish study. Retrospective data were collected on 902 HIV-positive individuals (72% of whom were co-infected with HCV) seen between January 1998 and April 2000 in order to determine the immunologic and virologic impact of HCV infection on those initiating HAART. There were significant differences in baseline HIV characteristics between the HCV-infected and HCV-uninfected individuals: mean CD4 count was 518 vs. 620 cell/mm³ and HIV RNA was 11,000 vs. 6,000 copies/mL, respectively. Similar proportions of individuals in each group were on HAART (92%), and there was no difference in drug adherence (83% taking >90% of pills).

After two years, there were striking immunologic and virologic differences between the two groups. HIV RNA on average declined only 606 copies/mL (5%) in the HCV-infected group compared to 5,788 copies/mL (53%) in the HCV-uninfected group. Likewise, CD4 counts on average increased 53 cells/mm³ (11%) compared to 111 cells/mm³ (22%) in the HCV-infected and HCV-uninfected group, respectively.

While this study does not provide actual data on HIV clinical disease progression, it is interesting to note such striking differences in HIV surrogate marker changes. Accordingly, the investigators raise an interesting question: Would treating a co-infected person's HCV (regardless of liver fibrosis state) indirectly help combat the underlying HIV disease?

**Studies concluding “No”**

Data from the Johns Hopkins 1,742 person HIV cohort suggest that HCV does not affect HIV disease progression or survival. Hopkins researchers followed this cohort, 45% of whom were HCV-infected, from January 1996 to June 2000 in order to monitor endpoints such as CD4 cell decline to <200 cells/mm³, development of OIs, and death. HCV-infected individuals were older, more likely to be black (85% HCV+ vs. 65% HCV- and had past or present IVDU (85% HCV+, 15% HCV-), yet no differences were observed in baseline CD4 or HIV RNA.

At the end of follow-up, no difference in HIV clinical progression was observed in the HCV co-infected individuals. Initially, an increased risk of progression to CD4 <200 cells/mm³ and death was documented in HCV-infected individuals with baseline CD4 counts between 50 and 200/mm³. When HAART use and lack of HIV RNA suppression to <400 copies/mL were controlled for, however, HCV infection was no longer significantly associated with CD4 decline or survival. Of interest, impairment of CD4 cell recovery on HAART was also noticed in the co-infected individuals at Hopkins. With three studies documenting this fact, TAG believes that intensified research in the immunology of HCV co-infection is warranted.

Two additional studies presented at the meeting failed to document accelerated HIV clinical progression or increased mortality in co-infected individuals. French researchers followed 995 HIV-positive individuals (58% of whom were co-infected with HCV) for 3 years. No significantly increased risk of AIDS or death was noted in the HCV-infected individuals compared to the HCV-uninfected individuals. And in a 504 person Seville HIV cohort, deaths due to liver failure were shown to have increased since 1997, but no significant difference in survival was observed between HCV-infected and HCV-uninfected individuals.

Opening up the debate of whether HCV alters HIV clinical progression adds to the never-ending list of questions in HIV/HCV co-infection clinical and basic research. In this fledgling field we desperately need large, collaborative, multicentered natural history co-infection studies (as well as treatment trials) in the U.S. and abroad—and the financial resources to implement, follow, and properly carry them out.
**Diseños Para Vivir**

**Los Veteranos del Clínico, del Gobierno, Industria, ASOs, Y Fármacos Buscan El Equilibrio Entre Datos y Droga**

Lamentando monoterapia virtual

En enero que el Antiviral Endroga el comité Consultor del FDA reunió para discutir el diseño del ensayo para la terapia de objetos salvados en la infección de VIH. La TAG Yuette Delph estaba allí y preparó este informe.

La reunión, menueada por Roy Gulick de la Universidad de Cornell, se convocó para enfocar en asuntos clínicos de diseño de ensayo para los individuos infectados de VIH que han limitado antiretroviral las opciones terapéuticas. Heidi Jolson, Directora de la División de Productos de Drogas Antivirales, notó que el interés de FDA estaba en el registracional antes que los ensayos de la estrategia del tratamiento y eso para el propósito de la reunión, el "altamente tratamiento experimentado (HTE) a población" se referiría a los individuos que carecieron o habían perdido la respuesta a dos o más regímenes de HAART y que tuvo la experiencia con uno o más miembros de cada clase de drogas.

Martin Schechter de la Red Clínica canadiense de Ensayos dio una vista general de opciones de diseño de ensayo en adultos. El notó que como individuos movieron del naïve del tratamiento para salvar, heterogeneity de población aumentado, pero ese heterogeneity sólo cuestiones si las variables son fuertemente prognóstico. El preguntó si deslumbrador en ensayos de objetos salvados introdujo más tendencia que previno, cuando podría secar la ventaja de la adherencia de un brazo con carga más bajo de píldora. El lamentó el hecho eses diseños de factorial son underutilized de woe-fully en la arena médica.

Carlton Hogan de la Coalición para la Terapia (CST) de objetos salvados dio la perspectiva de pacientes. El CST era incómodo con los diseños de intensificación que agregan simplemente a un agente nuevo a un regimen ya fallando ("monoterapia virtual") y él enfatizó que era esencialmente importante que la oferta de proactively de FDA limpie, la guía sin ambigüedades relacionada al uso de más que un agente de investigational. El CST abogó fuertemente que esa terapia de fondo sea optimizada de una manera basada individualmente en el genotypic y probar de resistencia de phenotypic (regimen (OBR) optimizado de fondo) y recomendado un diseño modificado de factorial encima de OBR. Con tres agentes nuevos (A, B, C) esto sería:

- A + B + OBR
- A + C + OBR
- B + C + OBR
- A + B + C + OBR

Tal diseño mejoraría las oportunidades del control de virologie en cada brazo, reducen el desarrollo de la resistencia a agentes nuevos así como también drogas de OBR, permiten que los efectos de agentes individuales sean discernidos, y pueden ser atractivo a participantes potenciales. Sin embargo, no hay brazo verdadero de control; puede ser difícil de atribuir los acontecimientos adversos a un agente particular con la certeza; y, si ciertas combinaciones fallan de lograr el control de virologie, participantes de estudio serían expuestos al toxicidad sin el beneficio proporcionado.

Dr. Jolson indicó que en 1999 el FDA había escrito a patrocinadores que indican que más que un agente de investigational podría ser usado y que la Agencia era extremadamente sostenedor de diseños de factorial. El FDA tuvo conciencia acerca de ensayos de intensificación en poblaciones de objetos salvados. Había apoyo general entre el entrepaño consultor para un diseño modificado de factorial en individuos de HTE.

Era el fieltro que lo seria unethical de matricularse los individuos profundos de objetos salvados en ensayos—ellos deben ser otorgados el acceso ensanchado o compasivo a agentes nuevos.

Michael Marco presentó la posición de TAG.

Daniel Vittecoq de la Agencia europea para la Evaluación de Productos (EMEA) Medicinales resumió el enfoque nuevo adoptivo por el EMEA a la matrícula de antiretroviral nuevo endroga con perfiles particularmente prometedores de resistencia o pharmaco-kinetic para el uso en individuos de HTE.

La fase los estudios II establecerían la dosis de la droga en personas de naïve de tratamiento o voluntarios negativos de VIH. Los ensayos de la fase III en individuos de HTE deben ser los dis-enos de la superioridad—o ensayos de la sustitución o intensificación. Habría una 2-4 evaluación de la semana de la eficacia y una 12-16 evaluación de la semana de la durabilidad y la seguridad. Los puntos finales primarios serían la proporción de cargas de viral de “undetectable” de lograr de participantes y = 0.5 diferencia log10 entre grupos.

Jim Rooney de la Colaboración (ICC) Intercompanías dio la perspectiva de la agencia. El notó algunos de las dificultades de ensayos que implica más que un agente: aislar el beneficio de un solo agente, la disponibilidad limitada de agentes nuevos, y de las interacciones y toxicities inesperados. El sugirió ese placebos no se debe usar a menudo en el objetos salvados que pone como ellos aumentarían magnificamente el carga de píldora.
Michael Saag de la Universidad de Alabama sugirió eses participantes del estudio sean estratificados antes de randomización según el número de opciones de tratamiento disponibles basadas en probar de resistencia. Esos con >3 opciones se randomizado recibir:
• OBR + placebo
• OBR + A
• OBR + B
• OBR + C
Esos con <3 opciones se randomizado recibir:
• OBR + A + B
• OBR + B + C
• OBR + A + C

Los miembros del entrepaño sugirieron diseños del ensayo que incluyen mecanismos para rescate temprano.

Etape 1: Agente nuevo “A” contra. placebo o ningún tratamiento por 1-4 semanas

Etape 2 (para ambos grupos): A + regimen optimizado de fondo (que podría incluir a otros agentes experimentales) para 12-16 semanas

Etape 1 proporcionaría la evidencia de la actividad de antiviral, tendría en cuenta controlar de resistencia y proporcionaría los datos a corto plazo de la seguridad y tolerabilidad.

En la discusión que siguió, los miembros del entrepaño sugirieron eses diseños del ensayo incluyen un mecanismo temprano del rescate para no responders. Los puntos finales sugeridos incluyen la disminución en la carga de viral, el aumento en el conde CD4, la proporción con la carga de viral de plasma debajo de detectabilidad y la cuesta de la decadencia de la carga de viral de plasma durante las primeras pocas semanas en el monoterapia o intensificación inicial de un regimen que falla. Los miembros de la comunidad enfatizaron la necesidad para un sistema para controlar la seguridad y toxicidad de agentes anuncian matrícula.


En los miembros del entrepaño sugirieron diseños del ensayo incluyen mecanismos para rescate temprano.

resistencia. Esos con >3 opciones se randomizado recibir:
• OBR + placebo
• OBR + A
• OBR + B
• OBR + C
Esos con <3 opciones se randomizado recibir:
• OBR + A + B
• OBR +B + C
• OBR + A + C

Dr. DeGruttola presentó en la elección de puntos finales para el objetos salva- dos estudio. El preguntó si estudie la retirada se debe contar como fracaso o como censurado, notar que cada análisis es probable influenciado. El recomendó hacer ambos analizar así como también más sofisticado analiza. La fase los estudios II establecerian la dosis de la droga en personas de naïve de tratamiento o voluntarios negativos de VIH. Los ensayos de la fase III en individuos de HTE deben ser los dis- eños de la superioridad—o ensayos de la sustitución o intensificación. Habría una 2-4 evaluación de la semana de la efcacia y una 12-16 evaluación de la semana de la durabilidad y la seguri- dad. Los puntos finales primarios serian la proporción de cargas de viral de “undetectable” de lograr de partici-
Los miembros de la comunidad eran unánime contra la aprobación de agentes con menos que 24 semanas de datos.
Desde los años 1980 hasta 1996, la incidencia de la enfermedad avanzada de CMV entre personas con SIDA se estimó para recorrer entre 10 y 40%.

El estudio pivotal de valganciclovir CMV
Valganciclovir es el ester de valine de ganciclovir de intravenous. Eran el año 1997, el FDA aprobara valganciclovir únicamente en datos de farmacokinetic que demuestran que un 900 mg dosis diaria (oral) de valganciclovir produjo la exposición comparable de la droga (área bajo la curva/AUC) a que del estándar dosis diaria de ganciclovir de intravenous de 5mg/kg. En lugares de la agencia requirió al patrocinador a conducir un randomizado la equivalencia clínica controlada de demostrar de ensayo entre valganciclovir y ganciclovir de IV para la terapia de la inducción de retinitis de CMV.

De 146 individuos que completaron la fase de 4 semanas de la inducción, 7 de 73 (~10 %) los individuos en el brazo de valganciclovir progresaron compararon con 7 de 73 (~10 %) en el ganciclovir de IV arma (95% de CI, -0.097, 0.100). Sesenta y cuatro y 63 individuos tuvieron no progresión fotográfica documentada en el valganciclovir y armamentos de ganciclovir de IV, respectivamente.

La seguridad
En Roche WV 15376, los datos de la seguridad estaban disponibles en 158 individuos. Los acontecimientos adversos eran semejantes para el valganciclovir contra diarrea de ganciclovir de IV (16% contra. 10%); pyrexia (13% contra. 11%); la náusea (8% contra. 14%); vomitó (11% contra. 6%). Como esperado, el ganciclovir de IV tuvo significativamente más infección relacionada de catheter, 11% contra. 2%. No había las diferencias significativas en anormalidades de...
Retinitis de citomegalovirus (CMV), un afectar de la enfermedad de viral la pérdida de ojos y causa de la visión, era una vez una enfermedad rara que ocurre sólo entre individuos con síndromes primario de inmunodeficiencia o desórdenes de autoinmunidad, receptores de trasplante de órgano y pacientes de quimioterapia de cáncer de inmunosupresor. En la gente con SIDA, retinitis de CMV está por lejos la manifestación más común, justificando por 77 y 90% de toda enfermedad de órgano de fin de CMV. En receptores de trasplante de médula de hueso, sin embargo, hay una mucha incidencia más grande de pneumonitis de CMV que retinitis.

Del 1980s a 1996, la incidencia de la enfermedad de órgano de fin de CMV entre gente con SIDA se estimó para recorrer entre 10 y 40%. En la era nueva de la terapia (HAART) altamente activa de antiretroviral, la tasa de la incidencia de CMV para los que tiene acceso a HAART—es hacia abajo bien debajo de 5%.

La enfermedad del órgano del fin de CMV ocurre tarde en el curso de SIDA y se asocia con condes CD4 extremadamente bajos. El conde CD4 mediano en personas con retinitis nuevamente diagnosticado de CMV es abajo 30 cells/mm3. Los síntomas principales de retinitis de CMV incluyen “floaters,” la visión enturbiada, las porciones perdidas de la visión y la luz que destellan/las chispas. Los cambios aún sutiles, tal como una pérdida secundaria de la visión periférica, puede indicar el desarrollo de retinitis de CMV.

Para la terapia de la inducción de CMV existe. En pesadamente individuos de inmunosupresor con retinitis de CMV, la terapia de la conservación de lifelong es recomendada en orden al lesions del asidero en un estado quieto. USPHS recientemente publicado/las pautas de IDSA indican eso “discontinuation of [CMV secondario] prophylaxis” se puede considerar en pacientes con un sostenido (por ejemplo, más que 3-6 mes) el aumento en CD4 + conde de lymphocyte T a más que 100-150 cells/mm3 en HAART.”

Valganciclovir es el ester de valine de prociclovir de intravenous. Eran el año 1997, el FDA aprobaría valganciclovir únicamente en datos de pharmacokinetic que demuestran que un 900 mg dosis diaria (oral) de valganciclovir produjo la exposición comparable de la droga (área bajo la curva/AUC) a que del estándar dosis diaria de ganciclovir de intravenous de 5mg/kg. En lugar, la agencia requirió al patrocinador a conducir un randomizado la equivalencia clínica controlada de demostrar de ensayo entre valganciclovir y ganciclovir de IV para la terapia de la inducción de retinitis de CMV.

Roche WV 15376 eran el estudio de registracional de patrocinador que uniformemente randomizado 160 individuos con retinitis de CMV para recibir valganciclovir (900 mg, oralmente, dos veces diario para 3 semanas seguidas por 900 mg diario para 1 semana) o ganciclovir de IV (5 mg/el kg dos veces diario para 3 semanas seguidas por 5 mg/el kg diario para 1 semana). Después que la comparación de cuatro semanas de la fase de la inducción, todo estudio se ofrece la terapia recibida de la conservación con abre valganciclovir de TAG (900 mg diario). El punto final primario era progresión de retinitis de CMV dentro de 4 semanas de iniciar fotografías de fundus de usar de tratamiento. La progresión se definió como movimiento >750 µM (por un >750 µM) o lesions nuevo de retinitis >750 µM. Estadísticamente, el estudio no era una comparación tradicional de cabeza a cabeza pero un no estudio de inferioridad accionó para probar ese valganciclovir no era 10% peor que ganciclovir de IV. Ambos armamentos se equilibraron uniformemente para el baseline demográfico y la posición de la enfermedad: ~90 % eran hombres; ~70 % estaban HAART activado; conde de célula de mediana CD4 era las células ~23; copias de mediana VIH RNA/ML era ~4.000; 24% de zona tenida 1 retinitis; y 25% de retinitis bilateral tenido.

De 146 individuos que completaron la fase de 4 semanas de la inducción, 7 de 73 (~10 %) los individuos en el brazo de valganciclovir progresó compararon con 7 de 73 (~10 %) en el ganciclovir de IV arma (95% de CI, -0.097, 0.100). Sesenta y cuatro y 63 individuos tuvieron no progresión fotográficas de IV ganciclovir no era 10% peor que valganciclovir.

El patrocinador se llevó a cabo también a unas 200 personas abren el estudio de la seguridad de randomizado, Roche WV 15705. Ningunas diferencias significativas en las toxicidades adverso de
La incidencia de retinitis relacionado de SIDA de CMV ha rebajado dramáticamente al menos de 5%; no obstante, valganciclovir ciertamente cambiará la administración clínica de la terapia de CMV. Con la administración más fácil, la adherencia al valganciclovir debe ser mejor que ganciclovir de IV y tener como resultado menos resistencia. Valganciclovir puede tener la promesa magnífica como prophylaxis para el retinitis de CMV. Hoffmann Roche debe continuar su positivo, la relación de collegial con el Grupo del Ensayos Clinicos para Adultos (AACTG) y lo sostiene a acumular y AACTG a3050 que completan, “Valganciclovir la Terapia por derecho [Prophylactic] para Cytomegalovirus.” Si los sitios internacionales en España, Australia, o Canadá se necesitan ayudar con la acumulación, Hoffmann-La Roche debe ayudar en la financiación de estas unidades. Ultimamente, Hoffmann-La Roche debe dejar con sus individuos dirigidos de paciente erróneos de advertir de campaña de no discontinuar su terapia de conservación de CMV con ganciclovir oral aunque ellos están HAART y el ataques activados las pautas de discontinuación resumidas por el USPHS/IDSA. †