TAGline

From the Treatment Action Group (TAG):
A monthly paper of research and policy

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Little Leaps

Gilead 2-in-1 Opens Door To Impending One Pill Triple Combo

GSK's, a sort of snoozer

In early August the FDA announced the approvals of two fixed-dose combination (FDC) antiretroviral drug products. FDCs are combinations of two previously approved drugs (à la the Combivir or Trizivir model) in what is understood to be a more convenient form: in both cases, one pill a day. The two new FDCs are GlaxoSmithKline's Epzicom (abacavir+3TC) and Gilead's Truvada (tenofovir+FTC).

These approvals, which allow for one fewer (in the case of Truvada) to three fewer (in the case of Epzicom) pills per day, promise to lessen pill burden for one component of HIV therapy. But neither represents a stand-alone regimen; they still must be taken with additional antiretroviral(s) in order to constitute an effective regimen. An FDC that combines all needed antiretrovirals into one pill is ultimately preferable (and is said to be in development by a surprising collaboration between BMS and Gilead). While these recent approvals represent a new and interesting option, both coformulations consist of previously available agents, and thus are not, in and of themselves, any great leap forward. Rob Camp reports.

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The Panel Speaks

In a letter dated 10/04/04, the PHS guidelines panel notified Dr. Paul Bellman of its decision regarding the "ban" on hydroxyurea:

"Since hydroxyurea is not approved for [the treatment of HIV], we have decided to remove it from the new guidelines revision... anticipated to be available... at the end of October."

Alice K. Pau, Pharm.D.
Executive Secretary, Panel on Clinical Practices for the Treatment of HIV Infection, Public Health System, Department of Health and Human Services

NOTE TO READERS/AVISO A NUESTROS LECTORES EN ESPAÑOL: As our translator leaves on indefinite sabbatical, we have temporarily suspended the Spanish translation of *TAGline*. We apologize to our hispanohablante readership and hope soon to return to a reliable, real-time bilingual service. The silver lining to this otherwise unfortunate turn of events is that it has freed up our middle column for a new follow-on feature which ties into last month's detailed look at Big Pharma's growing stranglehold on the research and care of HIV/AIDS.

This new column will feature each month a short bio of one power-wielding KOL (Key Opinion Leader) and what are oftentimes distressing overlaps between the medicine and monetary sides of his or her research and treatment activities. After the proposed title for this column, "Shill Factor," scored poorly among focus groups, we chose the more ambiguous "Double Duty": caring physician/researcher by day; ravenous pharma whore by night. The winner of our inaugural profile was virtually unanimous (although the competition was naturally quite keen). The man who along with Miami's Peggy Fischl, got this whole game going. Coming next month. †

Treble Damages

Vaccine Scientists Struggle To Come To Grips With the Field's "Berlin"

Technologically challenged

The AIDS Vaccines 2004 Conference was held from August 30-September 1 in Lausanne, Switzerland, the first of these meetings to be held outside the US (the first two were in Philadelphia in 2001 and New York City in 2003). Unlike many recent conferences which have concluded without any clear highlights or obvious signature issues to mark them, the Lausanne conference is likely to be remembered for spotlighting several key themes of broad relevance to the AIDS vaccine field.

Firstly, the disappointing immune responses seen with the International AIDS Vaccine Initiative's DNA-MVA candidate capped a growing concern about the prospects for vaccines based on current DNA and MVA platforms. Secondly, there was widespread agreement that the recently adopted ELISpot assay for assessing T cell immune responses based solely on production of the cytokine interferon-gamma is not providing a complete picture of vaccine-induced T cells.

Thirdly, reports from human trials suggested that the ability of macaque models to accurately pre-

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"Epzicom is a laser-based radio system used in inter-galactic android battles—by robots from francophone families."

"Oh well, Epzicom sounds like a hiccup."

-- U.S. treatment activists with too much time on their hands

Epzicom is an FDC of the antiretroviral drugs abacavir sulfate (Ziagen) 600 mg and lamivudine (Epivir) 300 mg. Epzicom is approved based on a large well-controlled clinical study (CNA30021 or Zodiac) that showed that abacavir dosed once daily had similar antiviral effect as abacavir dosed twice daily, both taken with lamivudine and efavirenz. *(For a complete listing of trials, please see www.treatmentactiongroup.org.)*

Epzicom is active against HIV in a variety of different patient groups. But use of abacavir (one of Epzicom's components) has been associated with potentially fatal hypersensitivity reactions in a growing number of patients.

TAG sees no cost or safety benefits for Epzicom over Combivir, and we caution against GSK's petition to place Epzicom as a first-line backbone. TAG believes that the company's application for approval of Epzicom for treatment of HIV infection in adults and adolescents was correctly approved by the FDA. However, the FDA should carefully monitor the company's education programs for both doctors and patients.

Studies of Epzicom leave some uncertainty about the relative benefits for it compared to other marketed NRTI backbones. In deciding whether to use any abacavir-containing regimen, physicians and patients should be aware that the existing double-nucleoside combinations of AZT/3TC (Combivir) or AZT/FTC, d4T/3TC (or d4T/FTC), TDF/FTC *(Truvada, see page 4)*, AZT/TDF, etc. may be as useful as Epzicom, without the risk of hypersensitivity or the "low genetic barrier" that could lead and has led to excess virologic failure.

TAG sees no cost or safety benefits to the use of Epzicom, and we caution against GSK's petition to place Epzicom as a first-line NRTI backbone.

Safety/Tolerability

In studies like CNAAB3005, common adverse effects for the ABC group were nausea (42%), headache (45%), malaise/fatigue (100%), diarrhea (27%), vomiting (25%) rash (80%) and fever (60%). In the Zodiac study, adverse events of grade 2 (mild) or greater are reported in 65% of those taking Epzicom once daily.

There were a number of failures and losses in both groups (ABC QD vs. itself BID): 10 vs. 8 virologic failure, 13 vs. 11 adverse events withdrawals, 11 vs. 13 "other" (consent withdrawn, protocol violation, clinical progression, changed therapy, other other). BID vs. QD had about 5% more CD4 gain. Treatment discontinuations in both groups hover at 24%. Add that to clear virological failures, and 30% of the original patients did not finish the one-year study.

Is ABC a (safe) alternative for lipodystrophic events?

Cholesterol and triglycerides went up significantly more in the ABC groups than in the AZT groups in CNA30024. AST and absolute neutrophils also went up. Although all these measurements were non-fasted (and the significance is thus not clear), at week 8, ABC was 50mg/dL higher in lipids!

In study ESS40001, ABC/3TC as background with an NNRTI, fasting total cholesterol rose 40 points, with a PI it rose 60, and with an NRTI it rose 32. Triglycerides all rose as well, with an NNRTI, +66, with a PI +90, and with an NRTI +70, all 3 classes going above the "safety zone" for NCEP III, calling for medical intervention. ABC/3TC does not help with these events, or with fat changes in any of the regimens.

Because 3TC requires dose adjustment in the presence of renal insufficiency, Epzicom is not recommended for use in patients with creatinine clearance <50 mL/min.

Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because Epzicom is a fixed-dose combination and cannot be dose adjusted, Epzicom is contraindicated for patients with hepatic impairment.

Hypersensitivity-Rechallenge= Risk of Death

Hypersensitivity (HSR) is a serious allergic reaction. Epzicom should be discontinued as soon as a hypersensitivity reaction is suspected. Epzicom or other abacavir-containing products must not ever be restarted following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death. Information on this serious allergic reaction has been updated in the Epzicom package insert as well as the patient Medguide/Warning Card.

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Erratum

Due to a production snafu at our printing house, some subscribers were left without the final two paragraphs of one of the lead articles in the September issue. We regret the inconvenience and encourage those subscribers affected to take advantage of a re-printing of those final paragraphs below. Thank you for your understanding. --MB

A Call to Arms

Veteran NEJM Editor Takes on Big Pharma As No One Before; Calls for Sweeping Reforms

'Weaning us off the dope'

... Early reviewers of the names and numbers note that acceptance of financial goodies (not to mention the unquantifiable triumvirate of fame, friendship and flattery) is not in itself evidence of objectivity's loss. In fact, without exception, the half dozen or so New York City HIV docs informally queried about their advisory and lecture circuit relationships with Big Pharma were eager to point out that they moonlighted for "all the major drug companies" with HIV products expressly "to avoid any question of bias." Others note that Angell's scorched earth solution (barring anyone with pharma ties from key panel posts) would only be self-defeating. Were financial ties to drug companies an automatic disqualifier, the argument goes, there'd be only empty chairs at empty tables. (Angell disagrees.)

For the time being, the only remedy deemed workable is that of disclosure requirements—ironically, what appears to have sparked Angell's fiery exposé in the first place. But, as she is quick to point out, does the mere act of disclosing financial ties to industry then render them acceptable? In the best of all worlds, certainly not, but it looks like that's all we have for

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Party Pooper

"I find it hard to imagine that a system this corrupt can be a good thing, or that it is worth the vast amounts of money spent on it. In addition, we have to ask ourselves whether it really is a net benefit to the public to be taking so many drugs. In my view, we have become an overmedicated society."

Marcia Angell, MD
"The Truth About the Drug Companies: How They Deceive Us And What To Do About It," (Random House, 2004)

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now (and what made pages 8-9 of this issue possible). While the major journals and a couple of the med-ed/CME web sites are doing a reasonable job of highlighting industry ties, professional associations, the ACTG, the FDA Antiviral Advisory Committee and some less reputable treatment information providers make it difficult if not impossible to know who's writing what for whom. TAGline *welcomes comments, corrections, updated disclosure and other information at tagnyc@msn.com.* †

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achieve in the world we live in today, but the world belongs to all of us to change.

Five years ago, doctors, nurses, and many other people told me and my friends that access to antiretrovirals was an impossible dream. Recently, Thailand announced that it would provide antiretrovirals to all who need it, starting with 50,000 people by the end of this year. Today, I urge all of us to dream of a day when our world will be filled with love, sharing and peace. And I believe that when we dream together, our dreams come true. †

The Agony of Bangkok

Thai Activist Exhorts Conference Crowd To Stand Firm Against U.S. Patent Regime and 'Masks of Fake Concern'

'Trading away health'

... Four years ago, Thai people with HIV/AIDS asked the government to use a compulsory license for ddI, but the government was too afraid of trade and other sanctions from the U.S. Ultimately, we took Bristol Myers-Squibb to court and won the right to produce tablet-form ddI, locally. In the final judgment, the Thai Court ruled that, because patents can lead to high prices and limit access to medicines, patients have the right to sue the patent holder. This was a very important battle that we won.

Governments and corporations hate activists because we know what they are up to, and we are pulling the masks of fake concern from their face to reveal their true nature. But to me, activists are to be honored. Activists are my true friends. They stand by my side when I face discrimination and injustice. They have the courage to stand up to those in power who use their positions for their own benefit. They are the ones who can help provide a way forward to fight AIDS and injustice in this world.

"Access for all" is the theme of this conference and the dream of many of us here. Yes, it's not easy to

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In Zodiac the incidence of HSR was higher than what had been reported in earlier studies. HSR is currently reported at <5%. This has now risen to 9% (vs. 7% in the BID group). The clinical meaning of this is that 90/1,000 persons will experience hypersensitivity. In light of this, FDA is requiring GSK to work with the community (via conference calls, meetings, etc.) to help educate people on HSR and what to do about it.

HSR may involve a low-grade fever, nausea, vomiting, malaise and rash, in a minimum grouping of three of these. All five of these present upwards of 58% of the time in a 10-trial meta-comparison. Intensity of these symptoms tends to increase with duration of therapy, and resolves upon therapeutic discontinuation. In a safety analysis of Zodiac, Hernandez et al. showed that most symptoms occur within the first 6 weeks, median time to onset being 9 days.

"Truvada sounds like a brand of Hungarian cigarettes. Or did they simply retool BMS' Zrivada (the working title for atazanavir)?"

Truvada is a single pill containing 300 mg of tenofovir disoproxil fumarate (TDF) and 200 mg of emtricitabine (FTC). These two drugs were previously approved individually under the brand names of Viread in 2001, and Emtriva in 2003.

Summary

When administered separately, Viread is one pill once a day, and Emtriva is one pill once a day. Truvada is administered as one tablet once per day, and thus, represents a marginal improvement in pill burden over the two separate components. Like Epzicom, Truvada is not a stand-alone combination—it still requires additional antiretroviral(s) in order to constitute an effective regimen.

TAG agrees with the accelerated approval of Truvada for use, in combination with many—but not all—antiretrovirals, in the treatment of adults with HIV infection. Any triple nucleoside regimens, including those containing Truvada, are not recommended. Triple nucleoside combinations of any sort have not worked well, and are not recommended (without a fourth drug—either an NNRTI or a PI).

Studies of Epzicom leave some uncertainty about the relative benefits for it compared to other marketed NRTI backbones

Ziagen (ABC) and Videx (ddI) should probably never be used with Truvada, due to concerns about resistance and ultimately efficacy.

Discussion

The approval of Truvada is based on bioequivalence studies demonstrating similar pharmacokinetic parameters to the individual products. Efficacy results from studies using the combination of TDF and lamivudine (3TC) [3TC has many similarities to FTC] are being extrapolated to support the use of Truvada, specifically the Viread registration studies 903 (TDF+3TC+EFV vs. d4T+3TC+EFV) and 907 (TDF+standard background vs. placebo+standard background), and the Emtriva registration studies 301A (FTC+ddI+EFV vs. d4T+ddI+EFV) and 303 (FTC+stable background vs. 3TC+stable background).

Safety

Bone density

Since osteomalacia (softening of the bones in adults) was observed pre-clinically in rats, dogs, monkeys and juvenile monkeys, close monitoring for bone toxicity in humans was done. There was no evidence of bone abnormalities in two studies, 902 and 907.

The three-year results from 903 were presented this year at Bangkok and are also summarized in *JAMA*. Study 903 was a Phase III, blinded, placebo-controlled trial comparing TDF to d4T, with a backbone of 3TC+Sustiva. This was an international study, and 26% of the participants were women. Significant bone density decreases occurred during the first year with TDF; decreases leveled off after the first year.

The *JAMA* article and Bangkok abstracts summarize subgroup findings, which found significant hip (-2.2%) and spine (-2.8%) bone mineral density (BMD) decreases from baseline in women taking TDF (but not women in the d4T group). This analysis did not find significant BMD decreases from baseline in men taking TDF.

In a small study pre-approval, TDF showed BMD issues in children. The pediatric development process stopped. Now, five years later, Gilead promises development of a TDF pediatrics dosing. The liquid that was developed is not bioequivalent, so it will be a pill form. PACTG will begin a 100-person study of this by the end of 2005. Once again, children get short shrift (no pun intended). A Truvada liquid will not be developed.

Closer monitoring along with calcium and vitamin D intake should become routine in the HIV clinic, particularly for post-menopausal

women, people with extensive PI experience, and people over 50. Outside of HIV, other risk groups for BMD decreases include Caucasians, Asians, and people who are slender, and/or have a family history of osteoperosis.

Kidney

Phase III Viread studies excluded individuals with renal impairment. Subjects were closely monitored for evidence of renal toxicity. No nephrotoxicity was seen and changes in serum creatinine and phosphate were similar to those seen with placebo. However, clinical experience has since turned up evidence of kidney toxicity in some patients taking TDF.

In the 144-week data from 903, no one developed tubulopathy or Fanconi's syndrome (out of 600 patients). 4% of people on TDF had grade 1 serum creatinine toxicity, and less than 2% had grade 2. No other events were reported. Serum phosphorus was the same for both the TDF group and the d4T group, at 4%. All 10/296 patients who developed grade 2 or 3 serum phosphorus increases did so before week 48. Proteinuria increases were similar between groups, at 12% and 17% for grade 1, 6% and 7% for grade 2. Glucosuria, grades 1–3, was reported not above 1% in any group. Creatinine clearance quickened by 5 at week 144 for TDF, and by 19 for d4T.

In the European and Australian Expanded Access Cohorts, 0.3% and 0.6% of people had grade 3 or 4 elevations in serum creatinine and reductions in serum phosphate, although any report was 2.5% (all grades) at 6 months for creatinine, and 18.9% for phosphate abnormalities.

Ziagen (ABC) and Videx (ddI) should probably never be used with Truvada, due to concerns about resistance and, ultimately, efficacy.

People with abnormal renal function may need to lower the dose of TDF, which of course can't be done with Truvada. What may have to be done is a different timing of medications, TDF every 36 hours or 3 times a week (M-W-F) or never (for those severely renally impaired), while FTC stays QD, which means two different drugs and not the Truvada pill *(see package insert)*. A small Truvada study is planned in renally impaired people.

Liver

They have looked at hepatic impairment and there is no adjustment needed. There is a black box warning about HBV flare-ups in the HBV-coinfected population. Up to 25% of people when stopping TDF can get flare ups, including grade 4. People with HBV need to be "monitored more closely." Sequencing and safety/efficacy of FTC need to be studied in a coinfected population. A strategy for avoiding this isn't clear.

Pancreas

Pancreatitis can be a concern with TDF+ddI. TDF inhibits the phosphorylation of ddI, and as a result, ddI stays in the blood at a higher concentration than is safe. Even with ddI at a reduced dose (the recommended dose of ddI with TDF is 250 mg/day), women, people who weigh less than 60 kg, and women who weigh less than 60 kg all independently have increased risks for pancreatitis. People who already are on the lower dose (250 mg) should probably be lowered again to 125 mg, but there is no recommendation currently.

Skin

With FTC, skin discoloration has been seen in up to 6% of patients. Medium time to onset is 88 days (range 10-490 days). Resolution happens without changing treatment in some 17% of those affected. Although no one has discontinued due to this hyperpigmentation on the palms and/or soles, sometimes the tongue, sometimes "other" places, it has been seen in a higher rate in black patients (up to 13% vs. 6% overall). In Asians it is seen in up to 4% of people, and in Hispanics up to 3%. Caucasians get it much less (<1%). In an HBV trial (non-HIV), the incidence was some 2%, not broken down by race.

For the complete report, please visit our website.

Important reminder: Deaths from rechallenge after abacavir (i.e., *Ziagen*, *Trizivir*, *Epzicom*) hypsersensitivity reactions

Death has resulted in individuals who have been rechallenged with abacavir following a hypersensitivity response. In the Zodiac study of the fixed-dose 3TC/ABC (Epzicom), the reported incidence of hypersensitivity reaction (at 9%) was nearly twice the rate reported in earlier studies of ABC (at <5%)—which, Rob notes, may be simply due to closer monitoring, for which GSK has been "responsibly cautious."

GlaxoSmithKline has developed language recommending that patients who develop a hypersensitivity response while taking Epzicom be discontinued from therapy, and *never* re-challenged. The FDA has adopted this language in a black-box warning about hypersensitivity in all abacavir-containing products.

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dict vaccine immunogenicity (capacity to trigger immune responses) might be more limited than previously realized. Richard Jefferys prepared this summary for TAGline.

IAVI's DNA-MVA Disappoints

The major news story to emerge from Lausanne is that IAVI is unlikely to move their first vaccine candidates into efficacy testing. The vaccines, a combination of a DNA "prime" and modified vaccinia Ankara strain (MVA) "boost" (produced by a team at Oxford University led by Andrew McMichael and Tom Hanke), induced HIV-specific CD8 T cell responses in approximately 10-20% of a total of 205 volunteers participating in multiple phase I and II studies in the UK and Kenya, according to presentations in Lausanne. This fell far short of reaching the 60% or greater response rate that IAVI views as necessary to justify launching a phase III efficacy trial.

IAVI released a statement to coincide with the opening of the conference, noting that the remaining studies of the vaccines will be completed and some additional immune responses looked at. But "unless there are new immune response data that are dramatically different, IAVI will not develop the candidates further, and will focus on its other research and development projects."

The results with IAVI's MVA-based construct are sobering, given that there are over a dozen candidate HIV vaccines utilizing MVA as a vector.

In the hallways and around the coffee tables of the Beaulieu Conference and Exhibition Centre, people mulled the implications of IAVI's data for the larger vaccine field. In terms of DNA constructs, IAVI's is not the first to show disappointingly poor immunogenicity in humans: Merck, Wyeth Ayerst and others have reported similar findings. Merck also found no advantage to giving its DNA as a prime before subsequently immunizing with a different vaccine (in this case, an adenovirus vector) as a booster, echoing IAVI's experience with DNA/MVA.

A commonly expressed opinion holds that part of the problem with current DNA vaccines is related to dosage; several conference participants estimated that a DNA vaccine dose of at least 8 milligrams is needed to match the dose given to macaque monkeys in pre-clinical studies. Only the NIH's Vaccine Research Center (VRC) has attempted this high a dose in humans. And preliminary results suggest that it did not result in a significant improvement in the immunogenicity of the DNA vaccine compared to a lower 4 mg dose. However, it's also very difficult to inject this much DNA into a human being, and experiments using more than 8 mg are essentially impossible.

Researchers are continuing to explore ways to enhance the response to DNA vaccines at feasible doses, including using separate constructs to encode each vaccine antigen and incorporating cytokines and other potential adjuvants. IAVI's results suggest that these efforts will have to be successful if DNA vaccines are to become viable for human use.

The data on IAVI's MVA-based construct are sobering given that there are over a dozen candidate HIV vaccines utilizing MVA as a vector. The extent to which the poor results reflect problems with the specific MVA candidate as opposed to the MVA platform in general is a matter of debate.

The ability of the vector to express the HIV antigens it is carrying once in the body is influenced by precisely where in the MVA genome the genetic code for the HIV antigens is inserted, and it is believed that other MVA candidates may be able to express higher levels of their antigen payload than IAVI's construct. It remains uncertain, however, whether such improvements can raise the immune response rate to an acceptable level.

Another potential problem with MVA is the large size of the vector; some researchers believe that this skews the immune response toward the vector itself rather than the antigens it contains. A small phase I trial of an MVA-based HIV vaccine produced by Bavarian Nordic recently reported that all participants developed MVA-specific T cell responses, but only a

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RV144: A Flawed Trial Falls Victim To Changing Conditions
by Richard Jefferys

Shot in the Dark: IBT Pipeline 2004
by Richard Jefferys

Third International TB/HIV Community Mobilization Workshop
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Drug Pricing for Middle Income Countries
by Mark Harrington

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minority showed evidence of responses to the HIV *nef* antigen contained in the vaccine.

Analyses of MVA-specific responses induced in the IAVI trials have not yet been reported. While immunogenicity studies of additional MVA-based HIV vaccines are going forward, it is entirely possible that the shortcomings of the approach will eventually lead to its demise, sending a large chunk of the HIV vaccine pipeline down the drain.

Multifunctional T cell Testing Comes of Age

The current crop of HIV vaccine candidates primarily aim to induce CD4 and CD8 T cell responses targeting the virus, due the fact that effective methods for inducing neutralizing antibodies have yet to be discovered. In order to assess the potential of these vaccines, researchers have expended considerable effort on developing and standardizing assays for quantifying vaccine-induced T cell responses.

The most rigorously evaluated approach is the interferon-gamma based ELISpot, which counts the number of T cells capable of making interferon-gamma after brief stimulation with HIV antigens (this is the assay used in the IAVI studies described above). Over the past few years, new studies have been presented showing that measuring interferon-gamma production alone may underestimate the size of the vaccine-induced T cell population because some cells produce other cytokines.

In Lausanne this issue came to the fore, and there was widespread agreement that a broader assessment of T cell responses will be important in future studies. Among the assays under discussion are intracellular cytokine staining, which several groups have used to show that T cells producing IL-2 can make up a substantial proportion of the response to commonly utilized vaccines. Helen Horton, from the HIV Vaccine Trials Network, demonstrated that GSK's HIV vaccine candidate incorporating *nef*, *tat* and gp120 proteins induced a CD4 T cell response mainly comprised of cells capable of producing IL-2—*not* interferon-gamma. Stephen De Rosa from the VRC has previously presented similar findings from a phase I study of a DNA HIV vaccine.

A growing body of evidence suggests that sole reliance on measuring interferon-gamma production may understate the vaccine effect on T cell responses.

Researchers from Guiseppe Pantaleo's lab also showed data implicating IL-2-producing T cells as important components of the HIV-specific immune response in infected individuals. Extending previous work demonstrating an inverse correlation between the frequency of HIV-specific CD4 T cells making IL-2 and viral load *(see the recent review by Pantaleo & Koup, Nature Medicine 10: 806 – 810, 2004)*, Simone Zimmerli reported that long-term non-progressors (LTNP) possess significantly more IL-2-producing HIV-specific CD8 T cells than individuals with progressing infection.

Matthias Lichterfeld from Bruce Walker's group in Boston described a study that tracked the ability of HIV-specific CD8 T cells to proliferate both during and after primary HIV infection. Lichterfeld found that HIV-specific CD8 T cell proliferation was detectable during primary infection but subsequently declined as individuals progressed to chronic infection. The proliferative capacity of HIV-specific CD8 T cells appeared to be linked to the presence of IL-2-producing HIV-specific CD4 T cells, according to Lichterfeld, "providing evidence of a direct functional linkage between these two cellular subsets."

The technique used to measure proliferation in this study involves staining cells with a dye called CFSE prior to stimulation with HIV antigens. (T cells that are able to proliferate lose 50% of the CFSE dye each time they divide, allowing researchers to quantify the degree of CFSE loss as a marker of proliferative capacity using a flow cytometer-based assay.) This new technique is a considerable improvement over previous proliferation tests and is another candidate for use in vaccine studies.

Michael Betts from the Vaccine Research Center debuted data obtained using a newly developed "multi-parameter" assessment of HIV-specific CD8 T cell function. The assay developed by VRC allows simultaneous assessment of several CD8 T cell functions, including production of the cytokines IL-2, TNF-alpha and interferon-gamma, the chemokine MIP1-beta and expression of a marker known as CD107a (a surrogate for the cell-killing potential of CD8 T cells).

Betts was able to identify a befuddling 32 different "flavors" of CD8 T cell in humans based on their ability to perform differing combinations of these functions. In a comprehensive analysis of HIV-specific CD8 T cells in infected individuals, Betts found that the spectrum of functions appeared to be connected to the clinical status of the study participant. LTNPs consistently displayed a more "polyfunctional" CD8 T cell response; e.g., more of their

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HIV-specific CD8 T cells were capable of elaborating all five of the above-described functions compared to individuals with progressive disease. Betts noted that this difference did not depend solely on differences in viral load among the study participants.

In a closing "report-back" session at the conference, Clive Gray stressed that a take home message was that these types of comprehensive analyses of T cell function will be important to consider in future vaccine trials. While it's not likely to be feasible to employ every possible test, those that capture responses missed by interferon-gamma ELISpot (such as intracellular cytokine staining for IL-2 and/or TNF-alpha) were cited as candidates for the same rigorous evaluation and standardization that ELISpot has undergone.

Predictive Value of Monkey Model Comes into Question

Before beginning human studies, the ability of vaccines to induce immune responses is almost always evaluated in monkey models (most commonly rhesus macaques). MVA vectors have generally been reasonably immunogenic in these models, but the IAVI data described above suggests that the picture in humans is rather different. Merck also presented data in Lausanne that adds to this concern. Merck is developing an HIV vaccine based on an adenovirus vector (dubbed Ad5) that will shortly enter an efficacy trial *(see* TAGline, *July 2004 for more information on this study).*

One of the problems with Ad5 is that many people have been exposed to the virus (which occurs naturally in the environment and causes severe colds) and therefore possess anti-Ad5 antibody responses that can severely reduce the immunogenicity of Merck's Ad5-based HIV vaccine. Based on monkey studies, it appeared that this problem might be circumvented by giving Aventis Pasteur's ALVAC vaccine as a booster following Ad5 immunization. But Robin Isaacs presented data at the Lausanne conference showing that this approach did not show comparable success in humans: immunizing with Ad5 followed by an ALVAC boost induced similar HIV-specific T cell responses to those seen when immunizing with Ad5 followed by simply another Ad5 shot—regardless of the level of pre-existing anti-Ad5 antibodies in the study participants.

These results suggest that immunogenicity data obtained in macaques need to be interpreted very cautiously until they can be confirmed in humans. More encouragingly, Merck was able to report that their Ad5 vaccine containing the *gag*, *pol* and *nef* genes from HIV performed comparably in people to their original test construct that contained only *gag*. (There had been some concern that including additional genes might reduce the magnitude of the T cell response—and/or the percentage of responders—to each one, but that didn't seem to happen.) Isaacs confirmed that this "trivalent" vaccine will be utilized in the upcoming phase IIb efficacy trial that is slated to begin at the end of this year. Merck is also continuing to explore the vaccine potential of alternative types of adenoviruses (such as Ad24) that may be less affected by the problem of pre-existing antibodies than is Ad5. †

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