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Prof. Michael S. Saag

Dr. Saag received a B.S. in chemistry with honors in 1977 Tulane University and earned his medical degree from the University of Louisville. During medical school, he served for three years on the Medical School Admissions Committee and received the Presley Martin Memorial Award for Excellence in Clinical Medicine. He completed his residency and infectious disease and molecular virology fellowship training at the University of Alabama at Birmingham. During his fellowship training, Dr. Saag made seminal discoveries in the genetic evolution of HIV in vivo. He evaluated isolates of virus obtained from individual patients at different periods in time and cloned and molecularly characterized these isolates to determine the degree of diversity of co-existing viral variants and to describe their evolution over time (Nature, 1988). While working with Dr. Dismukes, Dr. Saag designed and led a multi-center national AIDS clinical trial on the management of cryptococcal meningitis. This study included 194 patients and demonstrated the role of oral azole therapy in the treatment of this disorder in HIV-infected patients (NEJM, 1992). During the last 6 months of his fellowship, Dr. Saag conceived the concept of a comprehensive HIV outpatient (1917) clinic dedicated to the provision of comprehensive patient care in conjunction with the conduct of high quality clinic trials, basic science, and clinical outcomes research. Within the clinic structure, he established a clinical trials unit, a data management center, and a Clinical Specimen Repository designed to support the activities of the newly established Center for AIDS Research at UAB. In essence, the clinic became a "hub" for the clinical, basic science, and behavioral science investigators within the Center by creating a dynamic interface between the patients and the investigators.

Since the establishment of the clinic, Dr. Saag has participated in many studies of antiretroviral therapy as well as novel treatments for opportunistic infections. He has published over 260 articles in peer reviewed journals, including the first description of the use of viral load in clinical practice (Science, 1993), the first description of the rapid dynamics of viral replication (Nature, 1995), the first guidelines for use of viral load in practice (Nature Medicine, 1996), the first proof of concept of fusion inhibition as a therapeutic option (Nature Medicine, 1998), and directed the 'first-in- patient' studies of 7 of the 25 antiretroviral drugs currently on the market (including indinavir, efavirenz, abacavir, and enfuvirtide). Dr. Saag has contributed over 50 chapters to medical textbooks, has served on the Editorial Board of AIDS Research and Human Retroviruses, Co-Edited a textbook entitled AIDS Therapy (Churchill Livingston, now in its 3rd edition, and currently serves as an Editor of the Sanford Guide for Antimicrobial Agents and the Sanford HIV Guide. He recently served on the Board of Directors of the American Board of Internal Medicine (and as Chair of the Infectious Disease Subspecialty Board), has twice served as a member of the HIV Disease Committee of the Medical Knowledge Self-Assessment Program for the American College of Physicians, and has served recently on the NIH Office of AIDS Research Advisory Council. Dr. Saag currently serves on the International AIDS Society-USA Board of Directors, is President-elect of the HIV Medical Association, as a member of the HHS Guidelines Panel on Antiretroviral Therapy, and on numerous state, local, and national committees. He was elected into the American Society of Clinical Investigation in 1997. Among his other awards, Dr. Saag has received the Myrtle Wreath Award from Hadassah, was listed as one of the top ten cited HIV researchers by Science (1996), and has been listed as one of the Best Doctors in America since 1994. He received the Outstanding Medical Research Achievement Award from the AIDS Task Force of Alabama, an Excellence in Teaching Award from the Medical Association of the State of Alabama, was named a "Health Care Hero" by the Birmingham Business Journal (2003), received a Service Award from the AIDS Survival Project in Atlanta (2003), was a 2004 honoree of the Birmingham Chapter of the National Conference on Community and Justice (NCCJ), a recipient of the Birmingham Chamber of Commerce Spirit of Birmingham Award (2005), was a recipient of the Leonard Tow Humanism in Medicine Award (The Arnold P. Gold Foundation), and was a recipient of the UAB Alumni Society Hettie Butler Terry Community Service Award (2007).

Research studies typically fall into one of two main categories:

1) Observational studies
Here researchers observe the effect of a risk factor, diagnostic test or treatment without trying to influence what happens. Such studies are usually "retrospective" — the data are based on events that have already happened. Most workplace health research falls into this category.

Cohort study:

For research purposes, a cohort is any group of people who are linked in some way and followed over time. Researchers observe what happens to one group that's been exposed to a particular variable.. This group is then compared to a similar group that hasn't been exposed to the variable.

Case control study:

Here researchers use existing records to identify people with a certain health problem ("cases") and a similar group without the problem ("controls"). Example: To learn whether a certain drug causes birth defects, one might collect data about children with defects (cases) and about those without defects (controls). The data are compared to see whether cases are more likely than controls to have mothers who took the drug during pregnancy.

Some strengths of observational studies:
This may be the only way researchers can explore certain questions. For example, it would be unethical to design a randomized controlled trial deliberately exposing workers to a potentially harmful situation.
But the results of observational studies are, by their nature, open to dispute. Example: A cohort study might find that people who meditated regularly were less prone to heart disease than those who didn't. But the link may be explained by the fact that people who meditate also exercise more and follow healthier diets.
2) Experimental studies
Here researchers introduce an intervention and study the effects. Experimental studies are usually randomized, meaning the subjects are grouped by chance. While not all controlled studies are randomized, all randomized trials are controlled.

Randomized Controlled Trial (RCT)
Eligible people are randomly assigned to two or more groups. One group receives the intervention (such as a new drug) while the control group receives nothing or an inactive placebo. The researchers then study what happens to people in each group. Any difference in outcomes can then be linked to the intervention.

Controlled Clinical Trial (CCT)
This is similar to an RCT, except that subjects are not randomly assigned to the treatment or control groups. This increases the chance for "bias"–that is, that people with similar qualities ended up in each of the groups which could influence the final results.
Some strengths of experimental studies:
The RCT is still considered the "gold standard" for producing reliable evidence because little is left to chance.
But there's a growing realization that such research is not perfect, and that many questions simply can't be studied using this approach. Such research is time-consuming and expensive — it may take years before results are available.
At CROI 2014, the AIDS Clinical Trials Group (ACTG) presented data of their massive, 1,800-patient randomized trial ACTG 5257, known as the ARDENT study. In this open-label study, participants received tenofovir/emtricitabine (Truvada) and were randomized to receive either raltegravir (twice daily), atazanavir or darunavir.
The group used the well-known ACTG endpoints in ARDENT. Virologic failure was defined as a viral load above 1,000 copies/mL between weeks 16-24, or a viral load above 200 copies/mL after week 24. Treatment failure was defined as discontinuation of randomized treatment components. This could have more relevance than initially thought, since we could be misclassifying cases of slow initial viral load decreases as virologic failures.
After 96 weeks, 80% of raltegravir participants had viral loads less than 50 copies/mL versus 63% in the atazanavir group and 73% in the darunavir group.
With regard to tolerability failure, raltegravir and darunavir were both superior to atazanavir. And when investigators analyzed the data on cumulative incidence of either virologic or tolerability failure, raltegravir was superior to both atazanavir and darunavir, while darunavir was superior to atazanavir.
Much of the differences in this study were driven by an unanticipated higher rate of discontinuations due to toxicity (elevated bilirubin and gastrointestinal toxicity) in the atazanavir arm (16%). This rate was higher than in previous studies of atazanavir such as the CASTLE (3%) and QUAD 103 studies (6%). Maybe part of this difference was because of the open-label

nature of ARDENT compared to the blinded design of CASTLE and 103.
Furthermore, raltegravir had significant advantages in lipid profile and effects on bone mineral density as assessed by DXA scans. Taken together, ARDENT and other studies are signaling a shift in the standards of care for first-line treatment, with the ascension of integrase inhibitors and the fading (perhaps to "alternate" status) of boosted PIs.
Moreover, this is the first time ever that we have a randomized study that shows that a twice-daily regimen is superior to two preferred once-daily regimens.

Stefano Rusconi:

I'm here with Prof Mike Saag from the University of Alabama, Birmingham, a specialist in infectious diseases. Two questions. The first is about randomized clinical trials versus cohort studies. It seems that in the Ardent study, the two approaches merge together. What's your opinion?

Prof Saag:

Well, I agree. First off, for me both types of data - the randomized clinical trial or a cohort - give useful information. We need to understand the strengths and limitations of each. For the randomized trial, the strength is that you can eliminate channeling bias - the choice of who gets therapy A vs B; and in a cohort, that is driven by the provider's decision in the first place and how they go forward. So there's a bias there. However, the cohort does give us a look at how the medicines work over a longer period of time, and it includes everyone, whereas a randomized trial will attempt to exclude. So in the Arden study they're attempting to do kind of both, where they have some randomization but also some longer term follow up, and that's a good thing. My personal view is that we need all the information. And that's the value of all this. And in the long run, what I'd love to see is that - as more and more hospitals and clinics are using electronic records - we kick the level of quality of data from what I call clinical quality, which is good for patient care day to day, to research quality where the gaps in data and the quality of data is increased so that we can look back at all kinds of patients over time.

Stefano Rusconi:

Thank you and second question: following on from your final comment, how do weight these prêt-à-porter cohort series and in this respect, how much does geography count?

Prof Saag:

Well, I think any single study out of one location isn't necessarily generalizable to other locations. So the more clinics and cohorts have representation from multiple geographic centers, the better it can be. So there are some that do that around the world, and in Europe and the United States there are different cohorts that are merging data. But the key is that once those data are cleaned and complete, then you have the opportunity for all types of analyses that can be done on a dime - you can do it very quickly. The thing is understanding what questions to ask and whether those questions can be answered by the data sets that are there. But when that criterion is met, then we can start answering all types of longer-term clinical questions, and that is the value of a cohort. But again, as your question relates, we want to be able to have geographic diversity so that we can say that the findings are generalizable.

Stefano Rusconi:

Ok. Thank you, Mike.