

Beyond B HIV 2008 Web Conference Question & Answer Session Transcript

Live Webcast: 06/05/08 ♣ Archive Webcast: 07/11/08 - 07/11/09

John Hackett, Jr. PhD: I am going to coordinate the questions. The first one pertains more to Dr. Bolivar. Accurate quantification due to HIV diversity is clearly an issue. What impact could this have for development of vaccines?

Hector Bolivar, MD: This is a critical point actually in the field of HIV vaccine today. Obviously a potential successful vaccine candidate needs to take into account all the different HIV subtypes and also the geographic localization of the different subtypes and assure as much as possible, that the chosen vaccine will provide protection against a broad HIV cross type population. The problem with this is that the virus mutates rapidly and the global redistribution of the virus is so dynamic, as we have seen today, it is very difficult from a vaccine design point of view to cope with all these variables accordingly. I think that it still is too early really to know for sure what will be the impact of HIV diversity on this elusive target of developing an effective vaccine, but obviously it is a very important consideration.

John Hackett, Jr. PhD: Next I will take a question that pertains more to me. Group O infections are relatively rare in the U.S., so what is the advantage to using an assay capable of quantifying them? Well, it is an interesting question and I think in some ways, it is a philosophical one. While it is true that group O infections are rare in the U.S., certainly for patients that are infected with these strains, it is critical to have an assay that can reliably quantify that type of virus. In my view, there is another equally important reason for an assay to be maximally capable of comprehending HIV diversity. If an assay can meet the challenge of the high level of sequence diversity observed between Group M and O viruses, it certainly increases the confidence that the assay can tolerate diversity between subtypes, or even within a subtype. In most cases, a physician treating a patient who is infected with a non-B strain or even a variant B strain, does not know

Beyond B HIV 2008 Web Conference Question & Answer Session Transcript

this up front. If viral load values are unreliable or erroneous, clinical management decisions can be compromised.

I am going to move on to the next question. Dr. Bolivar, this is more directed to you. If an assay detects, but substantially underestimates copy number, there could be severe consequences. How can this limitation be addressed in clinical practice?

Hector Bolivar, MD:

Probably there is not straightforward answer for this scenario. Unfortunately, unless the patient presents like the patient that I presented today without discordant viral loads and clinical scenarios, there is no way to know if a particular patient may be infected with a non-B subtype and probably with a false low viral load due to the limitations of a particular assay. If the patient is clinically stable, probably there is not any problem or major consequence for the patient. But, as I mentioned at the end of my talk, viral load guides the start of antiretroviral therapy. If we have a false low viral load, probably it is going to delay the initiation of therapy and this could be problematic, something that we could initiate earlier if the viral load was reliable and we are going to defer by a substantial amount of time. The other thing I would suggest to clinicians is to get familiar with the assays that they regularly use to know the limitations that these assays have. Especially in large urban areas some patients may be infected with non-B subtypes and they may present with discordant numbers. If for any reason there is a good level of suspicion that the numbers don't fit, it probably is important to note the patient's geographic background; if the patient is coming from another country, or recently was traveling, or any indication that he/she could be exposed to a non-B subtype, and in that case it would be important and probably a payoff to order a different assay or different technology, to try to properly quantify viral load.

Beyond B HIV 2008 Web Conference Question & Answer Session Transcript

John Hackett, Jr. PhD: There is another interesting question I guess I will address. We have been talking a lot about non-B strains and circulating recombinant forms, and the individual is wondering whether the issue of genetic diversity is restricted to non-B strains. Is there any evidence that subtype B strains can be underquantitated by virus load assays? It is an interesting question, and in fact is a very good point because all of these assays can be influenced by diversity, even within a subtype. There is at least one publication and a recent poster presentation that have raised this issue. The first is a poster that was presented by Dr. Hillyard's laboratory at the Pan American Society for Clinical Virology Symposium this April in Daytona, Florida. It was interesting; they did an analysis of performance looking at Monitor version 1.5 and the new TaqMan assay and identified one subtype B specimen that was underquantified by 2.7 logs by the TaqMan assay. So here is a new generation assay that was struggling in this case. Clearly genetics can influence performance. A second example is a publication by Damond and colleagues in Journal of Clinical Microbiology in October 2007. This paper showed examples of subtype B, in addition to CRF02_AG, CRF_13_cpx, subtype A, and subtype G strains that underquantified by the new TaqMan assay relative to their original test, Monitor v1.5. So there is no doubt that even the new real-time assays have the potential to be influenced by genetic diversity even within a subtype. It is important to keep in mind. Good question.

Dr. Bolivar, I will find another one more directed towards you. Do you favor any particular antiretroviral regimen for non-B subtypes?

Hector Bolivar, MD: Probably with the exception of not using nonnucleoside reverse transcriptase inhibitors in the case of HIV-2, it has been very well documented that HIV-2 does not respond properly to nonnucleoside reverse transcriptase inhibitors, there is not really indication at this point to any particular regimen for non-B subtypes. I presented a paper today

Beyond B HIV 2008 Web Conference Question & Answer Session Transcript

in my presentation, and there are other studies like this one that suggest there may be differences in the response to therapy as per HIV subtype. However, the knowledge about HIV diversity and antiretroviral therapy is still too limited to make a solid therapeutic recommendation based on HIV subtypes. I think the new information is useful in terms of genotyping and resistance that will be emerging, and I can probably argue that in the future we will be able to customize or tailor a little bit more of the therapy in relationship to HIV diversity. At this point, to answer the question, I do not recommend any particular antiretroviral therapy for any particular subtype.

John Hackett, Jr. PhD: One other question had come in relative your presentation. Dr. Bolivar, what do you mean by drug naïve?

Hector Bolivar, MD: These are patients that were never exposed to antiretroviral therapy. I probably should explain that for people that are not clinicians in the audience. It means the patient was never exposed to any antiretroviral therapy.

John Hackett, Jr. PhD: Another question addressed to me. The HIV viral load assays seem to be variable in detecting subtypes. How does one choose an assay that is appropriate for their population? There are a variety of different commercial assays available. Useful sources of information include scientific publications, presentations at scientific meetings, package insert information, the sales people that are selling the test to you, asking questions, asking for evidence of how their assay performs on divergent strains. These are all good sources. There are certainly a number of publications out now that are relevant to the current new real-time assays that would be worth taking into consideration when one is making a decision like this. I really believe that the most subtype- and group-independent performance you can get is valuable regardless of your

Beyond B HIV 2008 Web Conference Question & Answer Session Transcript

patient population. Why not have the added assurance that you can deal with divergent strains of HIV-1?

Dr. Bolivar, there is another question directed to you. Is there any indication to perform a subtyping of the virus as a component of routine baseline investigations for a newly diagnosed patient?

Hector Bolivar, MD: Not here in the United States at this point. This is not a routine test that we order. However, I know that probably some state's health departments may be considering this as a part of the initial evaluation of HIV patients. This is probably similar in a way to how we order a baseline antiretroviral resistance test before starting therapy. In the future we would probably order a subtype analysis to actually know what subtype is causing the infection in the patient. I know that in Europe, for example in France, due to the broad geographic origin of the population and the effect migration has not only on HIV, but in general on medical care. HIV subtyping is part of the initial clinical encounter with patients. I also know from the French sources that in the United Kingdom for example, also for the same reasons, there are studies going on in HIV diversity. So far it is not done here in the States, but I suspect that probably we will talk more and more about HIV genetic diversity in years to come as long as the AIDS epidemic continues, unfortunately at the same pace we have nowadays.

John Hackett, Jr. PhD: A good example of comprehensive HIV diversity surveillance is the European SPRAD program that I mentioned. I was recently at the Sixth European Drug Resistance Workshop in Budapest, and it is clear they are trying to capitalize on the sequence information that is available to monitor subtype diversity. It makes sense and would be a useful approach here in the U.S. to learn more about the patient population we are dealing with.

Beyond B HIV 2008 Web Conference Question & Answer Session Transcript

Another question here. I guess I'll try this one. How would we know if a patient is infected with a non-subtype B strain? This is a good question. One option, if you were getting a baseline resistance genotype, theoretically you could mine that sort of information from the data that comes back. The patient history could also provide important clues: risk factors, history of travel, if they are an immigrant or have a partner who is an immigrant from a country with non-B strains, it certainly should heighten your radar. Dr. Bolivar's case study provides an excellent example of recognition due to discordant lab results. It is unfortunate if we are in a situation where the CD4 counts have declined totally and there is no detectable virus load, but certainly this is a huge red flag that there is an issue and additional analysis is warranted. In the U.S. we are just on the front edge of the curve. In terms of overall diversity we are going to see more and more, and so awareness and thinking about it in terms of how it relates to the tests you are using is an important consideration.

Here's one. It is an easy one for me to answer. When do you anticipate the Abbott RealTime HIV-1 assay will be available in the U.S.? It was FDA approved last year, so it is currently available.

What is the prognostic difference between group B and non-group B subtypes? Dr. Bolivar, do you want to comment at all on this? That's kind of a tough one.

Hector Bolivar, MD: I probably mentioned this in one of the studies in my slides. There are a few studies like this one trying to prove that in terms of the rate of progression of HIV to AIDS, differences exist between subtypes, and some of the studies are showing that probably subtype A has a slower rate of progression as compared with any other subtype, but still these studies are small. We probably cannot generalize to other subtypes, but we will learn more about these as far as new information becomes available.

Beyond B HIV 2008 Web Conference Question & Answer Session Transcript

John Hackett, Jr. PhD: There is another question that I guess I can try to take a stab at. What method or system would you recommend for sequencing, and what are cut off values for viral loads for sequencing? I am going to assume this is intended towards commercial assays that would be available. Again, the only one I have experience with is the Viroseq HIV-1 Genotyping System, and I would say overall that this assay has worked very well across group M strains in our hands. As far as the ViroSeq cutoff, the U.S. claim is 2,000 copies per mL, although we certainly have had cases where we have successfully genotyped down to 500 copies per mL. The TruGene assay has performed fairly well too, and I believe the cutoff is in a similar range.