Ethical and Regulatory Considerations in Adolescent HIV Treatment and Prevention Research

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• There are no financial conflicts of interest to disclose.
Concurrent Licensure

• The goal of product development for the treatment and/or prevention of HIV in adolescents† ought to be concurrent licensure at the time these products are approved and marketed for adults.

• Our ability to meet this goal requires thoughtful consideration of the relevant scientific and ethical issues so that adolescent product development can be incorporated into or proceed alongside of adult phase 3 development.

† For the purposes of this presentation, adolescents are considered to be between 12 and 18 years of age.
When Should Adolescent Trials Begin?

- We need “proof of concept” for a sufficient prospect of direct benefit (PDB) to justify exposing adolescents to the known (and unknown) risks of the intervention (21 CFR 50.52).
- Adults should be enrolled prior to adolescents to obtain the necessary data in support of this judgment.
- The adult data necessary to support a sufficient PDB may be less than the level of evidence required to establish efficacy.
- Once *sufficient adult data* exist to make this judgment, pediatric development should proceed without further delay.
- Whether we need an “adequate and well-controlled” study in pediatrics depends on our ability to “extrapolate” efficacy.
Scientific Issues - Dosing

- We anticipate no differences between adolescents and young adults with respect to the pharmacokinetics (i.e., absorption, distribution, metabolism and excretion) of anti-retroviral drugs. Thus, the same adult formulation and dosing regimen can be evaluated in adolescents.

- Observed differences between adolescent and adult pharmacokinetics are usually explained by differences in adherence.

- Thus, one does not need to obtain intensive PK data from adolescents, but blood levels can be used as a measure of adherence (i.e., population PK samples, at most).
Scientific Issues – Efficacy/Safety

Treatment:

- Evidence of efficacy in HIV-infected adults may be extrapolated to adolescents, given the similarity of the disease and response to treatment.
- Dosing and “proof of concept” with respect to potential clinical benefit are established in early phase adult trials.
- A cohort of HIV-infected adolescents (> 12 years of age) can be included in (or run parallel with) an adult phase 3 trial in order to obtain sufficient safety data (e.g., impact on growth given potential for bone toxicity) and demonstrate a similar pharmacodynamic response (i.e., plasma HIV-1 RNA).
Scientific Issues – Efficacy/Safety

Prevention:

- Pre-exposure prophylaxis (PrEP) with oral (men and women) or vaginal† (women) products can be effective, provided they are used consistently.
- Although PrEP efficacy can be extrapolated from adults to adolescents, adolescent adherence of greater concern.
- If lack of adherence undermines adolescent efficacy, safety concerns (e.g., bone and/or renal toxicity) in an uninfected population may alter the balance of risk/potential benefit.
- To date, there are no data in support of (and some against) the hypothesis of “risk compensation” or “disinhibition.”

† Note: Vaginal microbicides are not usually referred to as PrEP.
Enrollment of Adolescents in HIV Vaccine Trial?

Selected Recommendations (consultation - August 14, 2007)

- Not enroll adolescents until after interim efficacy and cell-mediated immunity (CMI) analysis of adult data
  - Require trend in favor of experimental HIV vaccine
- If extrapolation appropriate, base adolescent sample size on descriptive CMI data from interim analysis
  - Descriptive comparison between adult and adolescent immune response data could serve as bridge for extrapolation of efficacy
  - Reasonable to increase adolescent sample to improve power to detect a significant safety signal at an incidence of <1-3%
- Extrapolation of efficacy would permit concurrent labeling based on supporting dosing and safety data.
Scientific Observations

• From a scientific perspective, adolescents may be enrolled into adult phase 3 trials or in concurrent adolescent trials provided there are data establishing a sufficient “prospect of direct benefit” to justify the risks.

• Risk/potential benefit may differ across the adolescent age range for treatment vs. prevention (e.g., ≥12 years of age for HIV treatment; ≥15 years of age for PrEP) given differences in age-related risk factors for sexually acquired diseases.

• A proper evaluation of adolescent safety requires a longer duration of observation (at least 6 months) given the potential impact, for example, on bone formation and growth.

• Adherence (i.e., assuring, measuring) of central concern.
Ethical Considerations

Then why can it be so difficult to enroll adolescents in (adult) HIV treatment and prevention trials?

- Logistically, adolescents who are HIV-infected or at risk for acquiring HIV generally are cared for in pediatric clinics (thus requiring a sponsor to set up a clinical trial enrolling both adolescents and adults in two different networks).
- Ethically, two issues are worth highlighting
  - Measures to assure adherence with the treatment or prevention regimen (such as financial compensation)
  - The ability of an adolescent to provide informed consent without parental permission and/or knowledge
Influencing Adherence

- Financial compensation is often limited to a “minimum wage” model (based on time) out of a misplaced concern that higher levels of compensation may undermine voluntary choice.
- Although financial compensation influences decision-making, the view that it “unduly” influences adolescent choice to enroll in an IRB-approved protocol rests on a faulty analysis of the concept of “voluntary choice.”
- However, there may be legitimate concerns about excessive levels of financial compensation (e.g., placing participants “at risk” of harm from others).
- In addition, compensation alone (in the absence of other positive behavioral interventions) may be ineffective in assuring adherence to the study regimen.
Influencing Adherence

• Rather than relying on usual tools for assuring adherence in a clinical trial, HIV treatment and prevention trials may need to incorporate interventions to improve “retention in care”
  – For example, attention to psychosocial development needs, inadequate educational attainment, limited health literacy, coping ability, structural environment and individual case management.

• Disclosure (versus confidentiality)? (some observations)
  – Disclosure of gel use to sexual partners in CAPRISA 004 was associated with a modest 4.2 % increased adherence (71.0 vs. 66.8 %, p = 0.03).
  – When adolescents viewed parents as supportive, they disclosed more and kept fewer secrets. Monitored adolescents did not provide information to parents, even when they accepted parental authority.
  – However, “outness” predicted physical health benefits for higher SES men but health problems for lower SES men.
Importance of Parental Support?

Figure. Proportion of Patients With Virologic Failure by Age Stratified by Parental Absence

The shaded areas indicate 95% CI bands.

Adolescent Consent

• When FDA adopted the “Additional Safeguards for Children in Clinical Investigations (21 CFR 50 subpart D) as an “interim final rule” in 2001, it did not adopt the waiver of parental permission found in 45 CFR 46.408(c).

• This decision generated some controversy, as the waiver had been (and is being) used to permit adolescent “consent” for HIV (and other) research absent parental knowledge and/or permission.

• In the Preamble to the Final Rule on 21 CFR 50 Subpart D, published in the Federal Register on February 26, 2013, FDA clarified the decision not to adopt the waiver of parental permission.
Comment Opposing FDA’s Decision

• “The comment cited the example of research studies using new therapeutic modalities for the human immunodeficiency virus (HIV) and the acquired immunodeficiency virus (AIDS) in the HIV epidemic in the late 1980s and early 1990s and stated that many adolescents who sought treatment for HIV requested that their diagnosis be kept confidential from their parents.

• The comment stated that such confidential treatment was provided to these adolescents based on State laws allowing physicians to treat adolescents for sexually transmitted diseases without parental involvement.”
FDA’s 2013 Response

“We recognize that mature adolescents may contract diseases such as HIV–AIDS and other sexually transmissible diseases, and that there are important issues relating to the confidentiality of treatment sought. We note that in some situations a State may grant certain classes of mature adolescents of a specific age the right to consent to treatments or procedures involved in a clinical investigation. **These mature minors would not meet the definition of children under § 50.3(o) and thus would not be subject to the requirements of this subpart.** Similarly, minors deemed “emancipated” by state law also would not meet the definition of children under § 50.3(o) and would not be subject to the requirements of this subpart. **Mature or emancipated minors would be allowed to consent to participation in FDA-regulated research without the need for parental or guardian permission.** Thus, we consider reliance on established state and/or local laws that establish an adolescent as mature and/or emancipated to be appropriate in this context.”

Federal Register. 78(38);Feb 26, 2013:12946 (emphasis added).
Definition of Child

• “Children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.”

21 CFR 50.3(o)

• The National Commission (1978), in framing this definition, intended State-based treatment laws to apply to research.

• The waiver of parental permission was included for when a parent/guardian should be disqualified as an appropriate decision-maker, not for when an adolescent was thought to be developmentally capable of providing informed consent or desired confidentiality (absent enabling State law).
Figure 3. Minor’s capacity to consent to HIV services, by type of service
STI, sexually transmitted infection

Concluding Remarks

• From a scientific perspective, adolescents ought to be included in HIV treatment and prevention studies during the adult phase 3 trials so that the product may be licensed concurrently in both populations.
• Consistent with the National Commission’s analysis, FDA is permissive in allowing local jurisdictions to apply State HIV/STI minor treatment laws to enroll HIV and “at risk” adolescents in these trials, absent parental permission.
• In addition to disputes about the applicability of State law, local decisions may be influenced by attitudes towards, for example, parental supervision vis-à-vis adolescent confidentiality, and the morality of adolescent behavior.
Thank you.