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Meeting the goal of concurrent adolescent and adult licensure of HIV prevention and treatment strategies

Michelle Hume¹, Linda L Lewis², and Robert M Nelson³

¹Department of Psychiatry, University of Wisconsin, Madison, Wisconsin, USA

²Clinton Health Access Initiative, Boston, Massachusetts, USA

³Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration, Silver Spring, Maryland, USA

Abstract

The ability of adolescents to access safe and effective new products for HIV prevention and treatment is optimised by adolescent licensure at the same time these products are approved and marketed for adults. Many adolescent product development programmes for HIV prevention or treatment products may proceed simultaneously with adult phase III development programmes. Appropriately implemented, this strategy is not expected to delay licensure as information regarding product efficacy can often be extrapolated from adults to adolescents, and pharmacokinetic properties of drugs in adolescents are expected to be similar to those in adults. Finally, adolescents enrolled in therapeutic HIV prevention and treatment research can be considered adults, based on US Food and Drug Administration (FDA) regulations and the appropriate application of state law. The FDA permits local jurisdictions to apply state and local HIV/sexually transmitted infection minor treatment laws so that adolescents who are HIV-positive or at risk of contracting HIV may be enrolled in therapeutic or prevention trials without obtaining parental permission.

INTRODUCTION

Historically, children and adolescents were viewed as vulnerable subjects who should be protected from the risks of research. While the ability of adolescents to understand and make decisions about research participation arguably mitigates concern about vulnerability related to comprehension, adolescents were commonly excluded from trials of investigational HIV therapies conducted earlier in the epidemic. The result was a paucity of data that might be used to improve the access of children and adolescents worldwide to essential HIV prevention and treatment strategies, rendering them vulnerable to unsafe and/or ineffective therapies. More recently, paediatric research has come to be seen as a moral imperative

Correspondence to: Dr Robert M Nelson, Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration, WO32–5152, 10903 New Hampshire Ave, Silver Spring, MD 20993, USA; Robert.Nelson@fda.hhs.gov.

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because children and adolescents may be better protected by establishing the safety and efficacy of paediatric therapies through ethically appropriate and scientifically rigorous research.¹

Infants and young children usually will have been infected with HIV at birth as a result of maternal-to-child transmission, whereas adolescents may be at risk of HIV acquisition through sexual transmission and/or injection drug use.² The transition from childhood to adolescence can be viewed as occurring at the onset of puberty, an age at which there may be an increase in sexual activity and/or experimentation with recreational drugs. Our focus is on this adolescent population who are at risk for or living with HIV as their ability to access safe and effective new drugs and biologics for HIV prevention and treatment would be optimised by concurrent adolescent licensure¹ at the time these products are approved and marketed for adults.³ Meeting this goal requires thoughtful consideration of the relevant scientific and ethical issues so that adolescent product development can proceed concurrently with phase III development programmes in adults. We survey the ethical and regulatory issues that must be addressed to meet the goal of concurrent licensure and argue that allowing adolescents to consent for themselves for therapeutic research on HIV prevention and treatment strategies is both ethically desirable and legally defensible.

ETHICAL AND REGULATORY FRAMEWORK FOR ADOLESCENT PRODUCT DEVELOPMENT

From an ethical perspective, children and adolescents should only be enrolled in a clinical trial if the scientific objectives cannot be met either through enrolling adult subjects who can provide informed consent personally or through conducting research using animal models. In addition, the risks to which children are exposed in a clinical trial without the possibility of direct therapeutic benefit must be low. When there is a prospect of direct benefit, children and adolescents should not be placed at a disadvantage by being enrolled in a clinical trial, for example, through exposure to an unnecessarily risky intervention or failure to receive a known effective treatment that may prevent significant morbidity or mortality. These ethical principles serve as the foundation for international guidance, such as Guideline 17 of the recently revised Council for International Organizations of Medical Sciences (CIOMS) guidelines.⁴ In the USA, these ethical principles are codified in the US Food and Drug Administration (FDA) regulations governing the protection of human subjects and the role of institutional review boards at Title 21 Code of Federal Regulations (CFR) parts 50 (including subpart D addressing children) and 56, respectively.⁵

In the USA, the Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products (21 CFR 50 subpart D) provide an ethical and regulatory framework for determining when studies in adolescents should be initiated. While some low-risk single-dose pharmacokinetic studies may present no more than a minor increase over minimal risk (21 CFR 50.53), waiting until sufficient adult safety data have accumulated to argue that a single dose presents no more than a low risk may delay the adolescent programme. An

¹Licensure refers to marketing approval of a product by the FDA.

alternative is to design a treatment study that offers a prospect of direct benefit that is sufficient to justify the risks (21 CFR 50.52). From this perspective, the adult data required prior to adolescent enrolment are ‘proof of concept’ preliminary efficacy and safety information to support the judgement that the intervention holds out a sufficient prospect of direct benefit to justify exposing adolescents to the known (and unknown) risks of the intervention. Once *sufficient adult data* exist to make this judgement, development of the product for use in adolescents should proceed without further delay.⁶ The level of adult data necessary to support a prospect of direct benefit determination is less than the level of evidence required to establish efficacy. However, more robust adult efficacy and safety data may be necessary to assess whether this prospect of direct benefit is sufficient to justify the risks.⁷ As the examples discussed later illustrate, adolescent enrolment in HIV treatment and prevention trials may often be considered at the end of phase II or during an interim data analysis in phase III of adult studies if a trend towards benefit of the investigational product is noted.

APPROACHES TO ADOLESCENT PRODUCT DEVELOPMENT

There are a number of methods for streamlining adolescent product development for HIV prevention and treatment products. Paediatric efficacy can be extrapolated ‘if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [such that] the Secretary [of HHS or designee] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies’.⁸ To date, all drug products for the prevention or treatment of HIV have similar pharmacokinetic and pharmacodynamic profiles in adolescents and young adults.⁹ As such, the adult dose and formulation of these products generally is suitable for adolescents, although some products specify a minimum weight for the adult dose that may exclude younger adolescents with lower bodyweights. Intensive pharmacokinetic sampling is not needed in adolescents, but adolescent studies frequently include population pharmacokinetic measurements to verify dosing assumptions. For other products, such as immunomodulators, there might be age-related differences in immune function that require more data in adolescent patients.¹⁰

Evidence of efficacy of antiretroviral therapy in HIV-infected adults is typically extrapolated to adolescents, given the similarity of the disease and response to treatment.¹¹ As such, the preferred approach in treatment studies has been to establish dosing and ‘proof of concept’ with respect to potential clinical benefit in early-phase adult trials, and then to initiate a concurrent adolescent trial to evaluate efficacy and safety. While adolescents could potentially be included in adult studies, this option may not be feasible logistically as adults and children with HIV often are treated through separate clinical networks. Absent this operational barrier, there is no salient ethical reason to preclude clinical trials involving both adolescents and adults. Also, evaluation of adolescent safety may only require 24 weeks of observation compared with 48 weeks in adults for an initial approval, provided that the adult phase II study (which is often 24 weeks in duration) did not reveal a safety concern. A separate adolescent trial may help to obtain sufficient safety data to assess the potential impact of treatment on endpoints such as bone growth and development and also

demonstrate a similar pharmacodynamic response (eg, plasma HIV-1 RNA) to support the extrapolation of efficacy.¹²¹³

Although the efficacy of preventive products such as pre-exposure prophylaxis (PrEP) or microbicides can also be extrapolated from adults to adolescents, there are concerns that adolescents may be a poorly adherent population, which may compromise effectiveness.¹⁴ If effectiveness is undermined by lack of adherence among adolescents, then safety concerns such as bone and renal toxicity from PrEP may alter the balance of risk and potential benefit. Although adolescents may experience less toxicity with a lower drug exposure, a subtherapeutic dose provides no preventive benefit and as such only exposes the adolescent to risk.

Given the known relationship between effectiveness and adherence in both HIV prevention and treatment modalities, assuring and measuring treatment adherence in clinical trials is a central concern.¹⁴ Some trials have reported an increase in treatment adherence when use of protective measures is disclosed to sexual partners,¹⁵ though generally these effects were modest. Rather than relying on the 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, providing support for psychosocial development needs, addressing inadequate educational attainment and limited health literacy, improving coping ability, making changes in the structural environment and providing individual case management may be more successful at assuring adherence than simpler measures based on financial compensation or medication monitoring. When adolescents viewed parents as supportive, they disclosed more and kept fewer secrets.¹⁶ Ideally, investigational protocols should be designed to encourage the adolescent to seek support from parents and/or caregivers, in addition to providing treatment, thus supporting the entire family unit while honouring adolescent autonomy and confidentiality.

The appropriate timing of enrolling adolescents in a clinical trial can be illustrated using the example of the MRK Ad5 HIV vaccine. The sponsor argued that adolescents should be enrolled when there is 'sufficient promise' to undertake an efficacy trial, out of concern that any delay in the licensing of an HIV vaccine for adolescents would prove detrimental to public health.¹⁷ However, the willingness to initiate a phase III study in adults does not per se provide the necessary proof-of-concept information to support a prospect of direct benefit. At the time the adult study was initiated, there were limited data in monkeys (using simian HIV) suggesting a reduction in viral load after HIV infection, but no data on preventing HIV infection. Although the hypothesis related to the role of cell-mediated immunity (CMI) in the efficacy of the vaccine appeared reasonable, there is no established immune correlate for protection from HIV infection. In other words, there was no immunological surrogate that could serve as a short-term marker of potential long-term benefit either in reducing HIV infection or in reducing the viral load set point should an adolescent become infected.¹⁷

On this basis, the FDA determined that there was insufficient prospect of direct benefit to initiate the study in adolescents and required that interim efficacy and CMI data from the adult study be evaluated. Further, the agency required a trend in favour of the experimental

HIV vaccine at interim analysis prior to the enrolment of adolescents. This step would not have jeopardised the concurrent licensure of an effective product because the number of adolescents enrolled in the study may not need to be of sufficient size to permit an assessment of efficacy within that subgroup. Rather, a descriptive comparison between the adult and adolescent immune response data could serve as a bridge for the extrapolation of efficacy. However, the pivotal trials of this agent were terminated early for lack of efficacy after finding at interim analysis that the vaccine may increase the risk of acquiring HIV infection.¹⁷

More recently, adolescents are increasingly studied concurrently with phase III development in adults. For example, Tivicay (dolutegravir; ViiV Healthcare) and Genvoya (a fixed-dose combination of elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide; Gilead Sciences) were both approved in patients aged 12 years and older at the time of initial US licensure.^{18,19} Small adolescent cohorts were evaluated concurrently with phase III studies in adults to confirm the pharmacokinetic and safety profiles were comparable to those characterised in the larger adult efficacy studies. However, larger phase II studies in adults are critical to defining the safety of the products. Smaller adult phase II studies of some drugs have led to a delay in the timetable for paediatric studies due to insufficient safety information to reach the acceptable risk–benefit assessment needed to initiate the adolescent studies.

ADOLESCENT CONSENT

Adolescents enrolled in therapeutic HIV research in the USA can be treated as adults, based on the application of FDA regulations and individual state law. FDA regulations define children in 21 CFR 50.3(o) as ‘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’.²⁰ The Department of Health and Human Services (HHS) definition has minor wording variations that do not substantively alter the meaning.ⁱⁱ In effect, FDA and HHS regulations defer to applicable state law in defining whether a minor is a child for the purposes of applying 21 CFR 50 subpart D. For example, all jurisdictions in the USA expressly allow some minors to consent to medical care for the diagnosis or treatment of sexually transmitted infections (STIs).²¹ These laws are intended to encourage adolescents to seek treatment for reproductive health concerns through protecting the adolescents’ right to privacy in reproductive health decisions. As HIV is predominantly an STI, adolescents should be allowed to consent for HIV treatment regardless of whether state law specifically mentions HIV. State laws may not address explicitly an adolescent’s right to consent to medical care for the prevention of STIs. However, the extension of treatment statutes to STI prevention would be consistent with the intent of such state laws to protect the health of adolescents.

In the research setting, FDA regulations at 21 CFR 50 subpart D require parental permission for the enrolment of children. However, this requirement does not apply to adolescents being

ⁱⁱThe HHS regulations found at 45 CFR 46.402(a) define children as follows: ‘persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted’.

enrolled in HIV treatment trials if state laws allow access to confidential treatment for STIs. Alternatively, some HIV studies conducted or funded by the HHS have been performed using a waiver of parental permission provision found in HHS regulations at 45 CFR 46.408(c). This provision allows parental permission for research to be waived if the ‘research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children)’. Research studies using new therapeutic modalities for the treatment of adolescents during the HIV epidemic in the late 1980s and early 1990s were specifically cited as using this exception. ‘Many adolescents who sought treatment for HIV requested that their diagnosis be kept confidential from their parents ... such confidential treatment was provided to these adolescents based on state laws allowing physicians to treat adolescents for sexually transmitted diseases without parental involvement’.²²

When the FDA adopted the additional safeguards as an interim final rule in 2001,²³ the agency did not adopt the waiver of parental permission.ⁱⁱⁱ In the Preamble to the 2013 Final Rule, the FDA clarified the decision not to adopt the waiver of parental permission, noting that adolescents whom state law allows to consent for themselves would not meet the definition of a child under subpart D, and hence would not be subject to the requirement for parental permission found under subpart D.²² As such, the FDA permits local jurisdictions to apply state and local HIV/STI minor treatment laws so that HIV-infected and ‘at risk’ adolescents can be enrolled in these trials without parental permission.

Local jurisdictions (and individual institutions) may vary in their willingness to apply state-based treatment laws to therapeutic research interventions involving conditions for which adolescents would have a confidential right to treatment. 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 perceived morality of adolescent behaviour. The view that state laws promoting access for adolescents to confidential STI treatment should not apply to research interventions does not serve the interests of adolescents who may wish to seek treatment for STIs in a clinical trial. The National Commission clearly intended treatment statutes for consent to general medical care to apply to therapeutic clinical research when framing the definition of a child.²⁴ In addition, the reference in the waiver of parental permission under 45 CFR 46.408(c) to abused or neglected children appears to limit the waiver to circumstances where a parent or guardian should be *disqualified* as an appropriate decision-maker. Although the National Commission included contraception and drug abuse as examples where parental permission may not be appropriate,²⁴ the waiver was not intended to be used as a general loophole to avoid obtaining parental permission as parents often are supportive and disclosure may be in the adolescents’ best interests.¹⁶ Rather than using a waiver of parental permission, the application of state-based treatment statutes would allow an adolescent to make an informed decision about HIV treatment and prevention interventions in a clinical trial without a requirement for parental permission.

ⁱⁱⁱThe agency’s decision not to adopt the waiver was initially controversial, and as such the rule was not finalised until 2013.

Critics may argue that using treatment statutes to allow adolescent consent for research activities may place adolescents at inappropriate risk by enabling them to consent, for example, to early-phase studies of drugs to treat and/or prevent HIV. Building on the National Commission's analogy to state-based adolescent treatment statutes, we would not extend adolescents' ability to consent to non-beneficial studies that do not offer the possibility of sufficient clinical benefit to justify the risks (such as early-phase studies to establish proof-of-concept or single-dose pharmacokinetic studies of drugs requiring multiple doses for a therapeutic course). In effect, treatment consent statutes should only apply to a research interventions that meet the criteria of 21 CFR 50.52, which requires that the intervention or procedure holds out a prospect of direct benefit that is sufficient to justify the risks, and that the balance of the benefits and risks of the research intervention is at least as favourable to the adolescent as available evidence-based alternatives. Using this approach, an adolescent would not be considered a child for the purposes of applying the additional safeguards found in 21 CFR 50 subpart D, including the requirement for parental permission; however, a research ethics committee would need to determine that the protocol nevertheless does meet the criteria for approval under 21 CFR 50.52. In addition, given the range of adolescent maturity and decision-making abilities, consideration should be given to providing access to a suitable adult living with HIV who can provide support and advice.²⁵ There may be other suitable approaches to balancing the duty to protect the confidentiality of an adolescent at risk for or living with HIV with concerns about adolescent capacity, and potentially conflicting duties to parents and the institution.²⁶

CONCLUDING REMARKS

Adolescents ought to have timely access to safe and effective drugs and biologics for the prevention and treatment of HIV. Concurrent licensure of a product for use in both adults and adolescents can be achieved, for example, through earlier enrolment of adolescents in clinical trials and the use of extrapolation, when appropriate. If, as in the USA, an adolescent has the legal right to consent (without parental knowledge) to STI treatment, adolescents should be able to consent on their own to being enrolled in HIV prevention and treatment trials that offer a sufficient prospect of direct clinical benefit to justify the risks. To eliminate any ambiguity, laws establishing the right of an adolescent to confidential STI treatment should be modified to explicitly allow an adolescent to consent to clinical trials under these limited circumstances. The application of STI treatment statutes to allow for confidential adolescent enrolment in HIV research protocols is consistent with our ethical obligation to provide equitable access to treatments that protect adolescent health.

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