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Improving the informed consent process among HIV-infected undisclosed minors participating in a biomedical research: insights from the multicentre nutritional SNACS study in Senegal

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Abstract

OBJECTIVES Providing research information in a manner accessible to minors participating in biomedical research is a major challenge. Guidance is dramatically lacking regarding best practices for seeking informed consent among undisclosed minors enrolled in HIV-related research. We implemented an improved informed consent process (IICP) and identified factors associated with understanding of the information presented to HIV-infected minors prior to their enrolment in a study.

METHODS We enrolled study participants attending 12 paediatric HIV clinics in Senegal. Children ≥ 7 years were provided with standardised research information using the IICP, which involves viewing a video and taking part in extended group discussions. Understanding was assessed by seven basic questions scored 1 or 2 points, with a maximum score of 11 points. A score of 9 or more points was defined as satisfactory understanding. Factors associated with understanding were identified using a stepwise logistic regression model.

RESULTS Overall, 112 children, with a median age of 12.9 years (IQR: 10.2–15.0), participated in the IICP, of whom 37% were HIV disclosed. 71% achieved a satisfactory understanding score and all gave consent to participate in the research. HIV-disclosed children were more likely to demonstrate satisfactory understanding than undisclosed children (aOR = 3.2, 95% CI: 1.1–9.6). Age, study setting and education level were not associated with satisfactory understanding.

CONCLUSION These findings provide practical guidance for the development of improved and friendly informed consent processes in research involving minors. The implementation of the paediatric HIV research agenda will require a standardised and operational definition of informed consent, integrating the issue of HIV disclosure.

keywords informed consent, paediatric research, HIV research, research information, ethics, adolescents, HIV disclosure, sub-Saharan Africa

Introduction

Achieving the UNAIDS ambitious target to end the AIDS epidemic by 2030 urgently requires further research in HIV prevention, treatment and cascade of care in resource-limited countries, particularly among children and adolescents [1, 2]. However, since young participants cannot legally consent to participate in research studies on their own

behalf, paediatric research raises a number of ethical concerns that require special attention. The process of informed consent requires that researchers obtain the agreement of the child or adolescent's legal representative, to whom the information is commonly directed, and the consent of the school-age minor, who should express their willingness to participate in the research [3, 4]. Over the past 20 years, considerable attention has been paid to children's

perspectives on research [5, 6], to their capacities to provide informed consent [7, 8] and to the rights and status of vulnerable children [9, 10].

In economically poor settings, seeking informed consent raises specific challenges in research investigating HIV infection or HIV-related conditions, primarily because HIV disclosure to children is generally rare, even among adolescents [11]. In addition, decision-making of young people living with HIV might be affected, as a long-standing connection with healthcare services and disease intimately intertwines with their daily life. In many instances, orphans live with surrogate caretakers who are not formally appointed as the legal guardians and might be viewed as illegitimate consent givers [12].

The requirements of institutional ethics committees vary considerably throughout the world, leading to a wide range of practices [13] and ultimately to a gap of practical and standardised guidance for researchers. In Senegal, the 2010 law on HIV/AIDS merely recognises parental written consent for minors' participation. It encourages providing research information to children as part of their participation in a study and to seek their consent, without, however, specifying their age, how to proceed or taking into account their HIV disclosure status [14]. A growing literature from impoverished settings offers stimulating and helpful contributions on adolescent participation in HIV research [12, 15, 16]. However, there remains a paucity of empirical data concerning the implementation of informed consent processes involving HIV-infected children in paediatric research in Africa, and in particular in situations involving children who are not HIV disclosed [17, 18].

Achieving informed consent in a way accessible to minors is another critical aspect of the ethical process of paediatric research [19–21]. The informed consent process should use understandable, age-appropriate language and vocabulary, and should unfold in an atmosphere where the children feel at ease to ask questions and voice any concerns [22]. In this context, a video presents many advantages: visually engaging, capturing the viewer's attention, manageable and consistently providing the same research information to all participants. Video tools have been successfully used in low literacy research settings, resulting in improved understanding and retention of research information [23, 24].

The SNACS study was an interventional, multicentre research programme designed to assess the effectiveness and acceptability of the WHO guidelines for outpatient nutritional rehabilitation among undernourished HIV-infected children and adolescents [25]. The study was implemented in Senegal after a report of a high prevalence of HIV-related wasting among children and

adolescents in Dakar [26, 27]. A low HIV disclosure rate, of fewer than 20% of children aged 10–14 years within the routine healthcare system [28], brought forth a major ethical dilemma of providing research information to mostly HIV-undisclosed children eligible to participate in a study with objectives directly related to HIV infection. This multicentre study posed another challenge in conveying standardised information, accessible to children and adolescents with a wide age range. An improved informed consent process (IICP), based on a video and extended group discussion, was designed and developed in close collaboration between the researchers and the healthcare staff and was deemed appropriate for children ≥ 7 years of age.

The objective of the present article is to describe the IICP and to identify factors associated with understanding of the research information in HIV-infected children and adolescents prior to their enrolment in the nutritional intervention. We hypothesised that the standardised and friendly approach adopted in the IICP would facilitate obtaining a satisfactory level of research understanding among children, irrespective of their individual characteristics, including their HIV disclosure status.

Methods

SNACS study protocol

The SNACS study enrolled participants under active follow-up for their HIV infection in 12 paediatric clinics (two in Dakar, the capital city, and 10 in decentralised settings), aged 6 months to 19 years and presenting acute malnutrition (wasting). Follow-up visits were bimonthly and included anthropometric measurements, monitoring of adherence to therapeutic food consumption and, at regular intervals, an assessment of its acceptability. The participants were monitored until they recovered from acute malnutrition. A blood sample was taken at enrolment and at the recovery visits.

Pre-enrolment procedures

Before enrolment, all children under active follow-up were screened for eligibility. During the initial screening visit, both parent/surrogate caretaker and child (≥ 7 years) received preliminary information on the study and on the IICP from the study physician (Figure 1). Information was based on a sheet produced by the researchers and clinic teams covering all aspects of the study: the purpose, the nature of constraints and the foreseeable risks and benefits of the study, the types of data collected and their future use, the voluntariness of participation and

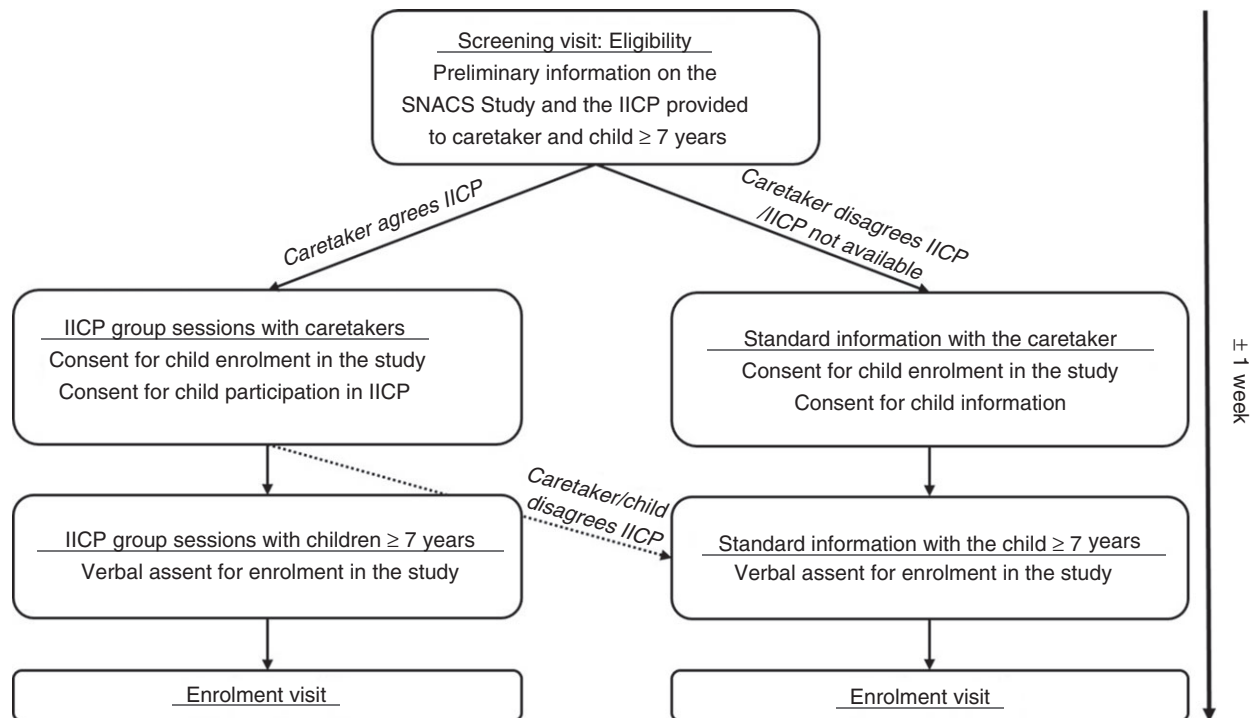


Figure 1 Per protocol model for pre-enrolment procedure in the SNACS study, Senegal (IICP: improved informed consent process in group session, standard information: individual text-based information using the information sheet).

the right to withdraw without consequence on the quality of care and follow-up routinely provided to their child. Caretakers were then invited to take part in a group session of the IICP. At the end of the session, written consent was sought for their child's enrolment in the interventional study as well as verbal consent for the participation of their child in a group session of the IICP. Verbal consent of the children was sought at the end of their IICP group session.

Implementation of the IICP with children

Healthcare staff received extensive training on implementation procedures. An IICP group session was composed of a small number of children, without their guardian, and was facilitated by the Senegalese research assistant (who attended all IICP sessions) and a healthcare worker (assigned to each study site). Sessions started by showing a 10-min long video followed by extended discussion, individual assessment of understanding and closed by verbal consent collection.

The first part of the video is adapted from an animated film produced by Médecins Sans Frontières – Luxembourg in 2010 (available at: <https://www.youtube.com/>

watch?v=LrRstT1iC0), which shows a young African child explaining the concept of malnutrition and its main causes and signs. In the second part, the character has been revamped and his dialogue was created using the content in the informed consent information sheet and with accompanying pictures and drawings illustrating the different sections of the protocol. In a monologue, the child presents the study objectives, the therapeutic food used, elements of the study (visits, measurements and actors), the advantages/disadvantages and the participant's rights. The voice-over narration was recorded in Wolof, with French subtitles, and was read over and listened to several times by the study's Wolof-speaking members to produce the most faithful translation possible. It was approved by all study actors before being distributed. The video was provided via a DVD and played using a laptop computer in a quiet room. In addition to the video, a welcome book was also developed and distributed to the children. This book contained the same information found in the sheet for caretakers but presented in a simplified, age-appropriate format.

The information contained in the video was reviewed and any questions that participants had were addressed in the extended discussion. Sessions were conducted

mainly in Wolof, or in a mix of French and Wolof depending on the French-speaking abilities of the children in attendance. These exchanges allowed the children to share their thoughts with each other and ask questions. Facilitators explained that therapeutic food carries virtually no risk for health and focused on constraints related to study procedures (expectations for study visits and adherence to the therapeutic food prescription, expected difficulties with therapeutic food consumption, the need for preventing family sharing of therapeutic food, blood collections, etc.) and individual and community benefits.

Next, the assessment questionnaire was administered individually to each participant by the research assistant, again in French or in Wolof according to the child's French-speaking level. A list of seven simple multiple-choice questions was used to assess understanding of the information. Each question addressed important points presented in the information sheet: the nature and objectives of the study (Q1 "What is malnutrition?" Q2 "What is food therapy?" Q3 "What are the objectives of the study?"), the study procedures and constraints (Q4 "How often should I come to the clinic?" Q5 "What will I have to do during the study?" Q6 "How often will I have to give blood?"), the voluntary nature of participation and the right to withdraw at any point (Q7 "What are my rights in the study?"). The questionnaires were corrected as a group with the facilitators providing fuller explanations.

Lastly, at the end of the session, the facilitators asked each child individually for their verbal consent. If they so desired, children could also sign their name on a designated space in the welcome book. Even though the children knew that their caretaker had previously given their consent, they were explained that they were free to refuse to participate in the study. HIV infection was not addressed in any of the study documents and tools because most of the children did not know their HIV status.

The IICP was implemented similarly with caretakers and children with the exception of the information sheet for caretakers and the welcome book for children. Both documents, which could be taken home at the participants' discretion, were provided only in French, as the official standardised written format of Wolof might not be accessible to many people in Senegal.

Data collection and analysis

The socioeconomic and clinical characteristics of the children were collected at the inclusion visit. Correct answers to the assessment questionnaire were scored +1 for questions 1, 2 and 3 (which involved essentially the

understanding of information) and +2 for questions 4, 5, 6 and 7 (questions which also included the notion of constraints or drawbacks). A score of 0 was given for an incorrect answer. The total and percentage of correct responses were calculated for each question and each participant. Understanding was defined as satisfactory when a child scored at least 9 of 11 points.

Socioeconomic and demographic profiles, as well as therapeutic history and severity of malnutrition, were investigated as explanatory variables for satisfactory understanding of the research information and were selected after controlling for collinearity. Associations from univariable analyses were assessed using the Wilcoxon rank-sum test, chi-square and univariable logistic regression, as appropriate. Factors associated with a satisfactory understanding of research information were identified using a stepwise logistic regression model. Explanatory variables with $P < 0.20$ from the univariable analysis were included in the multivariable model and excluded by the stepwise procedure at $P < 0.15$. Differences were considered statistically significant at $P < 0.05$. All statistical analyses were performed in SAS, version 9.3 (Cary, NC, USA).

Ethics

Ethics clearance for the SNACS study protocol, including the video and informed consent written documents, was given by the Ethics and Regulatory Committee and the Ministry of Health in Senegal. All parents or surrogate caretakers provided written consent.

Results

IICP implementation

From April 2015 to September 2016, the SNACS study included 184 HIV-infected children in 12 HIV clinics of whom 157 were ≥ 7 years. Three clinics declined participation in the IICP due to organisational constraints. These clinics provided standard text-based information to 45 caretaker-child pairs and assessment of understanding was not carried out following these individual sessions. All of the remaining 112 caretakers agreed to take part in IICP group sessions and subsequently consented for their child to participate in a group session and to be enrolled in the study. All children provided verbal consent to participate in the interventional study.

Overall, 112 children, with a median age of 12.9 years (IQR: 10.2–15.0), participated in 19 sessions of the IICP (i.e. six children per session on average). The average duration of a session was 90 min. All but

one child had been infected through mother-to-child transmission and 49% were maternal orphans (Table 1). Only 37% had known their HIV status, for a median duration of 11 months [5–29]. Some groups included both HIV-disclosed and undisclosed children, and all precautions were taken at every step of the IICP to minimise the risk of accidental disclosure of HIV status to an undisclosed child. Importantly, HIV-disclosed children were aware of the mixed composition of their group and were asked not to speak out about HIV infection. None of them mentioned HIV infection during the discussions. In addition, all children were aware of their malnutrition condition and informed of the objectives and content of the IICP prior to accepting the invitation to participate.

Children who took part in the IICP and those who received standard information did not differ according to any of their socioeconomic and demographic data; however, those who participated in the IICP were more likely

to know their HIV status ($P = 0.02$) and to present a virologic suppression on ART ($P = 0.01$).

Children's understanding of research information

Children performed well on questions concerning their understanding of malnutrition and food therapy, the frequency of study visits and the study objectives, with 93%, 93%, 90% and 92% giving correct answers respectively. Questions on data collection, the frequency of blood sampling and the participants' rights had lower rates of correct answers, 71%, 74% and 63% respectively.

Factors associated with satisfactory understanding of research information

Overall, 71% (79/112) of children achieved a satisfactory understanding score. To identify factors associated with

Table 1 Characteristics of HIV-infected children and their caretakers at enrolment in the multicentre SNACS Study,* Senegal

Characteristics	<12 years N = 43	≥12 years N = 69	All N = 112	P-value
Female	17 (40)	26 (38)	43 (38)	0.84
Study clinic	23 (53)	38 (55)		0.87
Dakar	23 (53)	38 (55)	61 (54)	
Decentralised setting	20 (47)	31 (45)	51 (46)	
In school				0.03
No	13 (30)	16 (23)	29 (26)	
Primary	30 (70)	43 (62)	73 (65)	
Secondary	–	10 (14)	10 (9)	
HIV status disclosed	3 (7)	38 (55)	41 (37)	<0.0001
Acute malnutrition				0.18
Moderate	28 (65)	36 (52)	64 (57)	
Severe	15 (35)	33 (48)	48 (43)	
On ART	35 (81)	66 (96)	101 (90)	0.02
Time since ART initiation, median (IQR), month	49 (18–65)	55 (19–89)	52 (19–85)	
Undetectable viral load on ART (≤50 copies/ml)	21 (60)	(32) (49)	53 (53)	0.30
Caretaker				0.83
Mother	20 (46)	31 (45)	51 (45)	
Father	5 (12)	6 (9)	11 (10)	
Surrogate	18 (42)	32 (46)	50 (45)	
Literate caretaker	27 (63)	30 (43)	57 (51)	0.05
Caretaker housing status				0.19
Home renter	21 (49)	25 (36)	46 (41)	
Homeowner	22 (51)	44 (64)	66 (59)	
Caretaker reporting income	25 (58)	43 (62)	68 (61)	0.66
Caretaker reporting food insecurity†	32 (74)	52 (75)	84 (75)	0.91

ART, antiretroviral treatment; IQR, interquartile range.

*Data are N (%) unless otherwise indicated.

†The Household Food Insecurity Access Scale – a list of nine specific questions about the availability and accessibility of foods and related worry for the household during the previous month – was used to assess food insecurity [45]. This access scale generates a 4-class variable of food insecurity – none, mild, moderate and severe. In this study, we used a binary indicator – food-secure (none) *vs.* food-insecure household (mild to severe).

satisfactory understanding of the information, we ran a stepwise logistic regression model with satisfactory understanding (yes/no) as the dependent variable. Explanatory variables were considered for inclusion in the model based on results from univariable analyses (Table 2). The multivariable analysis found that a higher proportion of HIV-disclosed children demonstrated a satisfactory understanding score than undisclosed peers (aOR = 3.2, 95% CI: 1.1–9.6) and that children in households owned by their caretaker outperformed those living with caretakers who rented their homes (3.5; 1.4–8.7). There was a trend towards a higher proportion of children in homes where the mother was still alive demonstrating satisfactory understanding ($P = 0.07$). Neither age nor education level nor study setting was significantly associated with satisfactory understanding in either univariate or multivariate analyses.

Discussion

Overall, 71% of children participating in the standardised IICP achieved a satisfactory understanding score. Systematic reviews of medical research conducted in sub-Saharan Africa report that among adult participants, there is a generally poor level of understanding of various items in the informed consent [29, 30]. In the absence of appropriate comparative figures, this result among younger people may be regarded as successful. While age, school level and setting are commonly put forward as risk factors [19, 31, 32], we found that none of them significantly affected understanding in this study. Earlier studies assumed that the poor understanding of most of the concepts associated with informed consent observed in children under 9 years of age was due to their developmental ability rather than questioning the content and presentation of the support material [20, 33]. However, a more recent study found that children as young as 6 years of age could understand potentially difficult and complex concepts when information was provided in an age-appropriate manner [34]. Our coupling of group discussion with the development and presentation of a friendly, age-appropriate video appears to have mitigated confusion and misconceptions arising from differences in maturity or education level. The strength of this conclusion, however, should be qualified, as most study participants had already reached adolescence. Furthermore, features of household and family stability which might enhance cognitive and psychosocial development were in fact associated with improved understanding in these children.

Group discussions under supervision of health staff may be particularly stimulating to children in this

sociocultural context. First, medical information is primarily conveyed from the health staff to the caretaker; subsequent interactions between the caretaker or health staff and the child are generally limited and unusual [35]. Second, such discussion groups were seldom used in decentralised routine care. For many of the children, the IICP provided them their first opportunity to meet peers and to share medical information. The group discussions also allowed children to speak up and be heard, thus making them more active participants in the research.

The relatively lower rate of correct responses to questions about data collection and participant rights shows the difficulties participants may have with the more scientific or conceptual aspects of research that may be unfamiliar to them [31]. The question about the participant's rights obtained the lowest score, an observation consistent with findings of a meta-analysis, based on 13 African studies published between 1998 and 2013, which reported that only 57% of adult participants understood their right to withdraw from a study [29]. Inadequate access to healthcare, social pressure and fear of losing care benefits if they withdrew were frequently reported [29, 30]. For the children involved in this study, who have routinely attended an HIV clinic since early childhood and who have established a relationship of trust with the healthcare staff, the idea that they could withdraw from the study might conflict with how they view the efforts of the healthcare staff in providing support and monitoring adherence to treatments and follow-up.

As only 37% of children were informed of their HIV status, maintaining confidentiality about the disease was a sensitive issue, even after the removal of references to HIV from all documents. None of the HIV-disclosed children, however, mentioned HIV infection during the group discussions, thus illustrating their capacity to observe secrecy around the disease [36]. Despite developing a process thought to be accessible to all, we found that HIV-disclosed children were more likely to demonstrate satisfactory understanding than their undisclosed peers, although the association was weak. Improvements brought to the process were likely to benefit all children and were even expected to mitigate various individual factors, including HIV disclosure, potentially underlying differences in understanding. Prior to participation in a research study, disclosed children may be better prepared to understand their role in the process and to project themselves in the successive steps of a research. HIV status disclosure per se facilitates intergenerational communication surrounding medical and psychosocial care. Furthermore, while not assessed in the study, it is likely that caretakers and healthcare workers felt more comfortable sharing and discussing research-related information

Table 2 Factors associated with satisfactory understanding of research information in HIV-infected children participating in an improved informed consent process,* Senegal

Effect	Univariable analysis†			Multivariable analysis‡		
	OR	95% CI	P-value	aOR	95% CI	P-value
Age§	1.2	0.5–2.9	0.60	0.7	0.2–1.8	0.43
≥12 years <i>vs.</i> <12 years						
Study setting	1.4	0.6–3.2	0.41	–	–	–
Dakar <i>vs.</i> decentralised						
In school	1.1	0.4–2.8	0.84	–	–	–
Primary <i>vs.</i> no						
Secondary <i>vs.</i> no	1.9	0.3–10.8	0.47	–	–	–
HIV status disclosed	2.3	0.9–5.7	0.07	3.2	1.1–9.6	0.04
Yes <i>vs.</i> no						
Mother alive	2.0	0.9–4.6	0.10	2.2	0.9–5.4	0.07
Yes <i>vs.</i> no						
Caretaker homeowner	2.7	1.2–6.3	0.02	3.5	1.4–8.7	0.007
Yes <i>vs.</i> no						
Undetectable viral load¶ (≤50 copies/ml)	2.0	0.9–4.7	0.09	–	–	–
Yes <i>vs.</i> no						

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

*One missing for multivariable model.

†Explanatory variables are included at $P < 0.20$ in multivariable analysis.

‡Explanatory variables are exited at $P \geq 0.15$.

§Age was retained in the multivariable model.

¶Detectable viral load (>50 copies/ml) modality included both ART and no ART children.

with disclosed children ahead of the IICP. Disease disclosure also proceeds together with a better understanding of the therapeutic issues, such as the importance of adherence to medication recommendations, of regular blood monitoring and clinic attendance [37, 38]. All these are concerns that similarly apply to the nutritional intervention.

The participation of HIV-infected children with undisclosed status in research related to HIV infection remains a major ethical issue. In such situations, the decision is left to the research stakeholders to offer specific provisions in the study protocols regarding the informed consent process. For obvious ethical reasons, all eligible children were enrolled in the SNACS study, as it would have been unacceptable to exclude children not informed of their HIV status from an intervention which was of benefit to their health and survival. By protocol, the healthcare staff at the clinics attended a practical training session conducted by an anthropologist (FH) who is an expert in the field of HIV disclosure to children [39]. Individualised disclosure plans were promoted and initiated within the study. In the US regulatory context, Barfield and Kane comment that while full disclosure may not be necessary for meaningful consent before the age of 14 years, it is recommended that the child and family be subsequently engaged in an HIV disclosure process with

the research team [40]. Furthermore, findings from a formative study in the Democratic Republic of Congo suggest that prior HIV disclosure should not be a mandatory component of any consent process for the involvement of minors in HIV-related research [17]. The authors advise researchers to consider a child-individualised disclosure plan to be initiated at enrolment with the caretaker and also to take into account the nature, procedures and duration of the study.

HIV disclosure is a complex and sensitive process [41] which should not be used in a way to satisfy an ethical prerequisite within the implementation of an HIV study, but should instead be pursued to enhance the child's well-being and to empower them in managing their illness. It is from this perspective that the WHO recommends that the HIV disclosure process could start with children as young as 6 years of age and should definitely be achieved before the child reaches 12 years of age [42]. Lastly, it is important to point out that low rates of HIV disclosure in low-income settings should not be an impediment to the development of necessary paediatric HIV research. Indeed, it should be part of the responsibility of biomedical researchers to implement or promote HIV disclosure during the course of the project, through a high-quality standardised process. Recent initiatives aimed at developing a comprehensive consent definition

are a crucial step towards better participation of minors in research [43, 44]. Nonetheless, the implementation of the prioritised research agenda to achieve the UNAIDS target in children and adolescents [1] will require the development of a standardised operational definition of informed consent that also integrates the issue of HIV diagnostic disclosure.

The interpretation and scope of these results may be limited by several design weaknesses. First, we acknowledge that the use of a closed and simple questionnaire, a choice driven by feasibility considerations, was more appropriate to measure information retention than to formally assess understanding level. We could have used a more complex questionnaire with a higher differentiating value. Alternatively, we could have asked children to teach back the information using their own words. Both methods would have better revealed whether they possessed in-depth understanding. The IICP was primarily designed to provide accessible information to participants using a friendly and interactive approach, and by doing so, to promote meaningful understanding of the research, rather than to be formally assessed. Hence, despite the limits arising from the assessment method, we are confident that most children reached a good level of understanding through this process.

Second, the protocol did not include a control group of children receiving only the standard paper-based process of informed consent for directly testing the hypothesis that the IICP significantly improved understanding. Although there are no other similar studies with which to compare, the level of understanding measured is likely to be greater than what one could expect within a standard process.

Third, in-depth qualitative analysis was not nested in the study to further investigate the factors, including the role and implications of HIV disclosure, operating within this IICP.

All these alternative designs would have allowed for a more robust and precise analysis of understanding and associated factors. Nonetheless, these findings provide insight into potentially important factors which should be considered in the development and implementation of appropriate approaches for seeking consent and improving understanding of research information in HIV-infected children and adolescents in sub-Saharan Africa.

Conclusion

An improved informed consent process consisting of a video coupled with extended group discussions proved effective in reaching a satisfactory rate of research understanding in HIV-infected children and adolescents. Our results, thus, support the implementation of such an

improved and friendly approach in seeking consent and understanding of information as part of the informed consent process in biomedical research involving children and adolescents in resource-limited settings. Further research is needed to explore the role that biomedical research should play in improving the context of care, particularly regarding the issue of HIV status disclosure in participating children.

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