

Guest Commentaries

Parental Disclosure of HIV Status

The functions of disclosure of HIV-positive status vary across the life span. For all ages, the hope is that disclosing one's status will elicit and mobilize social support on the part of family, friends, sexual partners, and the community. The fear is that disclosing will cause harm, whether through interpersonal rejection, family turmoil, discrimination, or assault because of the stigma and fear associated with AIDS. From the community perspective, a critical function of disclosure is secondary prevention of the spread of HIV. In this commentary, parent refers to the primary caregiver for the child or adolescent. Family refers to the network of mutually committed adults who reside with the child.

Parental disclosure of the HIV status of the child has rarely been studied in a systematic way. Parental disclosure has a number of elements:

1. Disclosure to the child of the child's HIV status
2. Disclosure by the parent to others of the child or adolescent's HIV status:
   with the consent of the child or adolescent
   without the consent of the child or adolescent
3. Disclosure of the HIV status of the parent or parents to the child or adolescent
4. Disclosure of the source of transmission to a child with vertical transmission

Developmental Considerations

The issues for HIV-positive children, adolescents, and adults about disclosure of the HIV status are different. Disclosure of diagnosis by the physician to the patient varies by stage of development of the patient. In the United States and Western cultures, the contemporary model of patient care is that patients are at the center of the process and, as such, have the right to full disclosure of their medical diagnosis, whether they are "ready" to hear it. This right is based on the assumption that patients should be participating in decisions about their care and not patronized. Adolescent programs for HIV treatment are also based on this adult model (1,2), although often a requirement at the time of disclosure is that a family member or trusted adult be present. Adolescent and child programs may differ from adult care in that, whenever possible, an effort is made to provide family-centered care. Only with children is disclosure of their HIV status withheld until the parent or family feels ready to tell the child and the child is judged ready to understand the diagnosis and cope with it. Here, the experience with childhood cancer patients (1) is used as one model for developing informal procedures or formal programs (3) for disclosure. Studies of disclosure to children indicate that disclosure increases as a function of age, with age 10 being the turning point (4–8).

Parents often express the fear that the stigma of AIDS will have a negative impact on the child and the family. In a review of disclosure of illness status to children and adolescents with HIV infection (2), the American Academy of Pediatrics states that children who knew their HIV status had higher self-esteem than children who were unaware of their status. Parents who disclose their child's HIV status to their child experienced less depression than those who did not disclose to their child.

There is little information available about parental disclosure to others with or without their child's consent. There are no published studies available that examine whether children disclose their HIV status to others with or without parental approval.

Who owns the process of disclosure can vary by age. Although all persons with HIV have the choice of whether to disclose their HIV status to others once it is known to them, only children and adolescents face the challenge of coping with family members who insist that the HIV diagnosis remain a family secret. Often times, caregivers forbid the child or adolescent from disclosing to anyone, including their best friend. At the other end of the continuum, children and adolescents may need to cope with family members who disclose their HIV diagnosis without their consent. This sometimes is an impulsive act, as family members seek relief (9) from the burden of this disease. Caregivers may go even further and decide to go public about their child's HIV status by speaking on talk radio shows or on television about their child's diagnosis.

Recently, Wiener et al. (10) at the National Cancer Institute reviewed in a systematic way the reasons that a family chose to make their child's HIV status public, e.g., appear on talk shows. There were nine children interviewed with 18 child–family dyads. Twenty-two percent of the children identified that telling a friend their diagnosis was the first step in going public. Fifty percent of the children believed disclosure to a friend was a positive experience. In 33% of the cases, the children reported that it was their parent's decision to go public, whereas 50% reported it was their own decision, and 17% reported it was a mutual decision. The question of whether the children, who reported that their parents made the decision to go public, had given their consent was not addressed in the article.

Clearly, the child's cooperation was needed. According to the children, the best thing about going public was doing new things, meeting celebrities, and receiving gifts and money. Eleven percent of the children reported that if they had it to do again, they would not go public. None of the

children reported that their relationships with their friends or families had worsened because they went public. Although the hospital staff perceived the children who went public as popular and well adjusted, these children reported that they perceived themselves as less competent socially, scholastically, and physically at baseline assessment and at the 4-year follow-up.

Children and adolescents may experience a profound sense of powerlessness when confronted with family members' decisions to disclose their HIV diagnosis to others without their consent. In a small but systematic study of this question with 15 adolescents who were infected by sexual transmission, using the Decision to Disclose (11) questionnaire, 11 adolescents with HIV disclosed their HIV status, in order of preference, to mother, sexual partners, father, best friend, and relatives (12). In two cases, the mother disclosed to others, but with the adolescents' permission. Only one adolescent had a parent (mother) who disclosed to others without her permission. This young woman was enraged and felt betrayed by her mother just at the time that she needed most to trust her and to depend on her. Managing the rage and feelings of betrayal then became the primary clinical issue, rather than her health care and maintaining functioning at school, with friends, and with her sexual partners. Clinically, we have observed parents threaten to disclose their adolescents' HIV status to their sexual partner(s) if they did not disclose on their own. In one case, a young woman who was pregnant was able to disclose her HIV status to her partner, the father of the child, before her mother did. In another case, the HIV-positive youth refused to disclose and his foster father called the family of his female partner and disclosed to her and to the family. These issues are explosive for the family who comes to rely on the medical team to help them negotiate these dangerous situations. Clinical observations indicate that in the worst outcomes, adolescents feel betrayed and a breach in the trust with the family occurs just when trust is needed most to help them cope with the illness. In rare cases, we have documented a brief psychotic break, episodes of running away from home, and psychiatric hospitalizations, precipitated by parental disclosure of HIV status to others without the adolescent's consent.

Children who have acquired the infection through vertical transmission face the challenge of a third and fourth phase in the disclosure process: learning of their mother's seropositive status and learning how their mother became infected. Family members avoid many of these disclosures; for the significant number of HIV-positive children who have survived into adolescence, avoidance is no longer possible as the HIV-positive adolescent comes to understand their disease and how it is transmitted. This process of parental disclosure of their own diagnoses and source of transmission is complicated by the stigma of AIDS, the fear of discrimination, and the social taboo of discussing drug abuse or sexual behavior with one's own children (13). Yet, such disclosures have been associated with the process of making permanency and guardianship plans for their children. Similar to disclosure of HIV diagnosis to the child, disclosure of parental HIV status also appears to be a function of age. In one study, mothers (87%) and fathers were significantly more likely to disclose their HIV status to adolescents (73%), compared with young children (23%). Eleven percent of parents disclosed to none of their children (14). Unfortunately, this same study found adverse outcomes for those adolescents whose mother's disclose their own HIV status to them. These youth engaged in more increased-risk sexual acts, smoked more cigarettes, and experienced greater emotional distress when compared with the children of mothers who chose not to disclose their HIV status. The reasons for these behaviors are not well understood. However, one study found that none of the adolescents who knew their parent had AIDS had disclosed this to a friend (15). This difficulty disclosing may further isolate the young person, thereby increasing their vulnerability to high-risk behaviors.

Practice Implications

Parental disclosure in its many facets should be a family process that is respectful of the concerns of the family and the needs of the children and adolescents. Facilitating this process should be part of posttest counseling and embedded, appropriately, in the developmental and psychosocial needs of the child or adolescent throughout their care by the treatment team. We concur with Wiener et al. (10) that it is the responsibility of the child's family, as well as the health care team, to help balance the family's motivations and altruistic desires in making private or public disclosures with the practical and psychosocial effects for the child or adolescent in each step in the disclosure process.

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Detection of Minimal Residual Disease in Bone Marrow During or After Therapy as a Prognostic Marker for High-Risk Neuroblastoma

For most of the 20th century, the outlook for patients with high-risk neuroblastoma (stage 4 and older than age 1 year at diagnosis and/or stage 3 tumors with *MYCN* gene amplification) has been dismal (1). Myeloablative therapy (2–4), especially if followed-up by 13-*cis*-retinoic acid (13-*cis*-RA) (4), has improved event-free survival (EFS) to approximately 40% at 4 years from diagnosis. Developing a means to distinguish those high-risk neuroblastoma patients for whom current therapy achieves long-term EFS from those in whom progressive disease will develop may facilitate interpretation of ongoing and future clinical trials. Markers that accurately predict a good outcome can be used to identify a subset of patients in whom future trials may explore a decrease in the intensity of cytotoxic therapy. Especially valuable would be reliable markers that predict failures with current therapy because such a group of patients could then be offered new (experimental) treatment modalities.

Therapy failures in high-risk neuroblastoma patients are likely caused by tumor cells developing resistance to chemotherapy (5). Most stage 4 neuroblastoma patients have marrow metastases at diagnosis (6), and marrow is a frequent site of recurrent disease (7). Therefore, sensitive (and, ideally, quantitative) detection of small numbers of neuroblastoma cells in bone marrow offers a means of assessing the efficacy of chemotherapy across a wider dynamic range than is possible with routine clinical methods. Recently, three different groups of investigators have reported that sensitive detection of neuroblastoma cells in bone marrow during or after therapy correlated with a significantly worse EFS (8-10). Two of these studies examined bone marrow during therapy, one study by the Children's Cancer Group used immunocytology (8), whereas a study from Japan used detection of tyrosine hydroxylase (*TH*) gene expression by reverse-transcription polymerase chain reaction (RT-PCR) (10). Both of these studies showed that persistence of detectable tumor in marrow after completion of induction chemotherapy was associated with a lower EFS rate. A third study showed that detection of *GAGE* expression by RT-PCR in bone marrow 24 months after completion of intensive chemotherapy combined with anti-*GD2* antibody therapy correlated with poor EFS (9).

Given that three different studies (using different methodologies) showed a correlation between detection of neuroblastoma in bone marrow and EFS, one might be tempted to begin using detection of tumor in bone marrow during or after therapy as a prognostic factor to identify subsets of patients. However, current and future therapies not used for many of the patients in the previous three studies could likely influence results. In the Children's Cancer Group study (4), patients received one of four possible different therapeutic combinations (chemotherapy only, chemotherapy plus 13-*cis*-RA, autologous bone marrow transplantation only, and autologous bone marrow transplantation plus 13-*cis*-RA). Currently, most patients with stage 4 neuroblastoma receive myeloablative therapy followed-up by 13-*cis*-RA and, in some cases, immunotherapy as well. It is possible that developing more effective therapy could decrease the significance of minimal residual disease (MRD) detected before completion of therapy; this is especially true for therapies used after the MRD is measured. Indeed, in the Children's Cancer Group study, MRD detection in marrow harvested for autologous bone marrow transplantation in patients who were randomized to not receive 13-*cis*-RA appeared to correlate with a poor EFS, but this was not the case for patients randomized to receive 13-*cis*-RA (8). In the study reported by Fukuda et al., patients did not receive postmyeloablative therapy, which could decrease the adverse prognostic impact of detecting persistent tumor earlier in therapy (10). Other differences in therapeutic approach (such as purging of tumor cells from marrow or peripheral blood stem cells) could also influence the impact on EFS of MRD that persists in bone marrow during induction therapy.

In contrast to measuring MRD during therapy, detection of tumor cells in bone marrow 2 years after completion of therapy (9) would seem to be less influenced by different therapeutic strategies used since the initial study. However, detection of MRD with RT-PCR in patients treated with a differentiation inducer (such as 13-*cis*-RA) could mean something quite different from detection of a neuroblastoma-associated gene expression (*GAGE* or *TH*) in the bone marrow of patients who were not treated with a retinoid. The mechanism of action for 13-*cis*-RA is induction of tumor cell differentiation and sustained arrest of tumor cell

proliferation (11). Although neuroblastoma cells that respond to 13-*cis*-RA in the bone marrow do eventually show undetectable tumor by routine morphology or immunocytology (11,12), it is possible that small numbers of viable (but terminally differentiated and thus, nonproliferating) tumor cells could persist in bone marrow for months to years after therapy, without leading to progressive disease. Conversely, the persistence of such detectable cells may identify those patients in whom late relapses will develop.

The recent reports linking detection of MRD in bone marrow to outcome in high-risk neuroblastoma are provocative, but additional studies are required to truly define this approach to prognostication. Except in the context of clinical trials, subjecting neuroblastoma patients to bone marrow aspirations solely for the purpose of evaluating MRD should not yet become a routine part of care for children with high-risk neuroblastoma. For patients in whom consideration is being given to treatment with experimental approaches aimed at eradicating MRD, detection of MRD would be useful in deciding on such experimental therapy. However, for the reasons outlined previously, detection of MRD in bone marrow after completion of therapy is not yet a clear indication for additional therapy. Moreover, there are currently no treatments proven in a randomized trial to be effective in preventing or delaying progressive disease in such a setting other then those already used for all patients, i.e., myeloablative therapy and 13-*cis*-retinoic acid.

A careful evaluation of the impact of MRD in bone marrow and blood before, during, and after therapy is planned as an integral part of the new high-risk neuroblastoma phase III trials in the Children's Oncology Group. Detection of MRD in the Children's Oncology Group studies will be performed at various times during therapy and will be performed by both immunocytology (8) and RT-PCR for multiple gene products (9,13–15). The large number of uniformly treated patients that will be studied in the Children's Oncology Group phase III trials will provide the statistical power needed to clearly define the prognostic value of detecting persistent MRD in marrow during therapy and after completion of therapy.

If persistent MRD in bone marrow is confirmed to portend a poor outcome, then a logical next question will be what should be performed to improve therapy? A number of novel approaches to treating neuroblastoma are being tested in clinical and preclinical studies (16–24). Developing markers to identify those stage 4 neuroblastoma patients older than age 1 year at diagnosis who are at high-risk for progressive disease with current therapy will facilitate design of clinical trials aimed at testing such new approaches. Indeed, the use of MRD detection in bone marrow may not only allow stratifying patients for such studies but also will provide a means for assessing the effect of novel therapies against MRD, without having to wait for the larger tumor burden necessary to quantify tumor by routine clinical methods.

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