# Unmet needs persist in pediatric HIV programs: Lessons from selected case studies in Uganda

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[1–7] and one case with nelfinavir [8]. These are both protease inhibitors, suggesting a class effect. Frozen shoulder has also been described before with barbiturate and isoniazid.

The current case report is the first to report complex regional pain syndrome affecting the hip in a patient taking antiretroviral drugs. It is also the first case implicating either elvitegravir or cobicastat (or a combination of the two). If other case reports follow, protease inhibitors will no longer be the only class of ARVs to be associated with the complex regional pain syndrome. A protease inhibitor cannot be responsible in this case, in which improvement was seen after stopping cobicistat and elvitegravir and there was no recurrence upon restarting his previous ART (which included the PI amprenavir). We note that of the 26 cases reported, 12 involved bilateral shoulder capsulitis [1–8], which is high compared with the literature data [9–11]. Our case had bilateral shoulder involvement as well as right hip capsulitis. This could also suggest an iatrogenic cause.

In conclusion, we suggest that elvitegravir and cobicistat be considered amongst the possible causes of capsulitis. The bilateral involvement could be more common in drug capsulitis. Other studies are necessary to further define the relationship among elvitegravir, cobicistat and protease inhibitors, and capsulitis. Stopping the drug in question seems to lead to rapid improvement in symptoms.

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### Conflicts of interest

There are no conflicts of interest.

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## Unmet needs persist in pediatric HIV programs: lessons from selected case studies in Uganda

Tremendous progress has been made in the management of HIV/AIDS in sub-Saharan African adults [1]. Pediatric HIV management, however, has unmet needs in early diagnosis and antiretroviral therapy (ART) [2]. The goal of care and treatment has progressed from prevention of mother-to-child transmission (PMTCT) to elimination of mother-to-child transmission [3]. The children with HIV early ART trial in South Africa demonstrated that early ART initiation can improve survival, reducing early mortality by 76% [4]. This led to the revision of WHO ART treatment recommending ART for children aged 2 years or less irrespective of their immunological profile. Recently, WHO has updated their ART treatment guidelines [1,5–8] recommending that all people living with HIV (PLWHIV), regardless of age, should be initiated on ART [8]. If fully implemented, this recommendation will markedly improve the quality of life of PLWHIV and raises the possibility of ending the epidemic. However, this hinges on early diagnosis and treatment, reaching out to those lost to follow-up (LTFU) and a stable supply and availability of antiretroviral drugs [9]. In an ongoing study investigating the role of nutrition as a determinant of

**Table 1. Summary of clinical and social characteristics of the four antiretroviral therapy-naïve cases.**

| Patient characteristics | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Sex | Female | Male | Female | Male |
| Age in completed years | 5 | 8 | 5 | 12 |
| Next of kin who brought patient to Mildmay Uganda | Aunt | Mother[a] | Grandmother | Sick uncle |
| Psychosocial status | Orphan<br>Had been staying with distant relatives, and she had been moving from home to home | Boy with a single parent<br>Had always been staying with his grandmother | Orphan<br>Residing with grandmother | Double orphan<br>Stayed at a pastor's orphanage and appeared to be a laborer |
| Healthcare of first entry point | Private clinic | Private clinic | Unknown | Mildmay center |
| Treatment received at the healthcare of first entry | Parenteral ceftriaxone, quinine and diclofenac then oral artemesinin/lumefantrine with no improvement | Parental phenobarbitone, rectal diazepam. Carbamazepine through a nasogastric tube but his seizures persisted. Later was started on parental amphotericin-B, ceftriaxone, ampicillin/cloxacillin, acyclovir and septrin prophylaxis | Parental ampicillin and gentamycin followed by ceftriaxone and cloxacillin, oral fluconazole, paracetamol, vitamin A and nutritional rehabilitation | Tenofovir, lamivudine, efavirenz and septrin prophylaxis |
| Presenting symptoms | Acute diarrhea and vomiting | Intractable seizures | Acute diarrhea and vomiting with progressive weight loss | Previous loss to follow-up for over a year; no medical complaints |
| Nutrition status | Severe acute malnutrition | Well nourished | Severe acute malnutrition | Well nourished |
| WHO staging | 4 | 4 | 4 | 1 |
| Clinical diagnosis | Profuse watery diarrhea, severe dehydration, severe pneumonia, extensive oral–pharyngeal candidiasis and possible disseminated TB | Cryptococcal meningitis | Oral candidiasis and severe bronchopneumonia | Asymptomatic |
| Clinical outcome | Died | Severe neurological sequelae | Died | Lost to follow-up[b] |

TB, tuberculosis.
[a]Child had been staying with his grandmother prior to illness.
[b]Attempts to reach the caregiver by phone were futile, and a home visit found that he had been sent back to his village and had dropped out of both HIV care and school.

immune function and pharmacological outcome amongst HIV-infected malnourished children in Uganda, we observed that the older children had been missed by PMTCT programs. The majority presented with critical illnesses and had a mortality rate of 22.5% compared with 1% in the younger age group. We describe four ART-naïve cases as examples of the 'forgotten children' who have missed the opportunity of PMTCT, early infant diagnosis (EID) and early ART.

A 5-year-old orphan girl, brought by her grandmother for care at Mildmay Uganda, was screened but excluded from the NOURISH study. She presented with vomiting, diarrhea, fevers and marked body wasting and was unable to take the study food supplementation.

On admission, she was critically ill with very severe respiratory distress. The weight-for-height *z*-score (WHZ) was less than −3 SD with a body weight of 10 kg, mid upper arm circumference of 11 cm and height of 108 cm with a BMI of 8.55. *Pneumocystis jiroveci* pneumonia was suspected. She had severe anemia, acute watery diarrhea, severe dehydration, extensive oral–pharyngeal candidiasis and nonedematous severe acute malnutrition (SAM). She died 24 h after admission with no further diagnostic work-up.

An 8-year-old boy was admitted with intractable seizures. He had been living with his grandmother when he developed an acute episode of high-grade fever for a day followed by intractable tonic–clonic seizures. He was taken to a nearby private clinic where an HIV test was positive and referred to Mildmay Uganda.

On admission at Mildmay Uganda, he was comatose (Glasgow Coma Scale – 5/15) and in *status epilepticus*. His anthropometry was normal and he was treated for acute pyogenic meningitis, but analysis of his cerebral spinal fluid revealed cryptococcal meningitis. A computerized

tomography scan of the brain showed enhancing lesions in the occipital and left parietal regions.

He was referred to Mulago National Referral Hospital, and there tuberculosis (TB) treatment was initiated. He emerged from his coma but had severe neurological sequelae. He developed SAM and was started on nutritional rehabilitation feeds. The $CD4^+$ T-cells count/percentage and viral load at baseline were 5 (1%) and 195 650 copies/ml, respectively, and 2 weeks after anti-TB drug initiation, he started ART.

A 5-year-old girl was admitted to Mildmay Uganda having been brought by her grandmother who requested an HIV test. The grandmother reported that she had been 'sickly' for several months with progressive weight loss, persistent fevers, poor appetite and a long-standing cough.

On examination, pallor and marked wasting were noted with a weight of 10 kg, a height of 91.5 cm (WHZ $< -3$ SD and BMI of 11.9) and classified as nonedematous SAM. She had extensive oral candidiasis, reduced air entry bilaterally and a tachycardia of 198 bpm.

Pulmonary tuberculosis was considered, treated for bronchopneumonia and presumptive bacteremia. On day 9 of hospitalization, she suddenly deteriorated with intractable vomiting and passed away.

A 12-year-old boy, a double orphan, was enrolled in the NOURISH study. He had been staying at a pastor's home/orphanage. He was brought to Mildmay Uganda, previously LTFU with no complaints, and his anthropometry were normal. His $CD4^+$ cell count and viral load were 1132 cells/ml and 194 777 copies/ml, respectively. He was reinstated into HIV care and was to return after 2 weeks, but did not return. Table 1 summarizes the clinical and social characteristics of our four cases.

## Discussion

Delivery of a robust pediatric ART program is complex and requires many disciplines to work together. Only 35% of HIV-exposed infants (HEIs) access EID services in the first 2 months of life in Africa. Pediatric ART provision has therefore lagged behind adult ART programs [2]. Major obstacles facing scale-up of pediatric HIV care include shortage of trained pediatric providers, no systematic effort to identify and follow HEIs who are LTFU, limited availability of quantitative virologic testing, missed opportunities for testing children, insufficient advocacy and understanding of ART complexity and changing political priorities [10]. The number of children who need to initiate ART has markedly increased, as every child who is HIV-positive should initiate ART irrespective of immunological status.

It is clear that majority, if not all, HIV-positive children have challenging psychosocial backgrounds. As illustrated in one of the cases, even when children are enrolled in care, these psychosocial issues delay diagnosis and initiation of treatment and lead to LTFU.

These cases highlight some factors that will make the UNAIDS 90-90-90 treatment target difficult to achieve and need urgent attention [3]. To make progress in the next 4 years, we need to actively look for the 'forgotten child' and follow-up these children by strengthening outreach and community-based services [11]. As many children are first seen in private clinics, we need to empower them to provide test and treat strategy.

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Consent: Ethical approval to carry out this study was sought and received from the following institutes in that order: Trinity College Dublin IRB Faculty of Health Sciences Ethics Committee in October 2014, IDI Scientific Research Committee in December 2014, the Higher Degree for Research Ethics Committee School of Public Health in December 2014 and the Uganda National Counsel of Science and Technology in January 2015. Study site approvals were received from Mildmay Uganda in January 2015. Informed consent was sought and received from the primary carer, and in addition for children aged 8 years and above provided assent to participant in the study except for the critically ill patients whose assent was done when out of danger if they survived.

### Conflicts of interest

There are no conflicts of interest.

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## Kidney transplant outcomes in HIV serodiscordant recipient pairs

Kidney transplantation has been successfully employed in $HIV^+$ patients with end-stage kidney disease [1]. However, allograft survival rates are less favourable than in the general kidney transplant population [2], which may relate to the high incidence of delayed graft function [3], acute graft rejection [2,4,5], or infection of the graft with HIV [6]. Use of less intensive immunosuppressive regimens and expanded criteria donors, drug–drug interactions between antiretroviral and immunosuppressive regimens, and persistent immune activation and inflammation may contribute to the increased rate of graft rejection [2,4,5,7–9]. In the absence of randomized clinical trials, useful insights may be gleaned from analyzing donor/recipient characteristics and graft outcomes in HIV serodiscordant recipient pairs of deceased-donor grafts.

$HIV^+$ recipients of a deceased-donor kidney allograft between January 2005 and December 2013 were identified in a national cohort study in the United Kingdom [4]. We used the date of birth, transplant date, ethnicity, sex, and transplant centre to identify these cases and the $HIV^-$ recipients of the other kidney graft from the UK transplant registry held by National Health Service Blood and Transplant. Information supplied by National Health Service Blood and Transplant included survival, graft survival, graft rejection status, and details of immunosuppression at 3 months, 1 year, and 5 years. Donor and recipient characteristics were compared using nonparametric statistical tests. Kaplan–Meier estimates were used to determine patient and graft survival. Cox-proportional hazard regression analysis was used to determine factors associated with allograft rejection in the first year post-transplantation.

In total, 51 (89%) of the 57 $HIV^+$ deceased-donor recipients in the cohort study were identified in the Registry; 40 of these belonged to an $HIV^+/HIV^-$ recipient pair. The median interquartile range donor age was 48 (37, 57) years. $HIV^+$ recipients were younger (43.5 vs. 52.0 years, $P = 0.009$) and more likely to be of black ethnicity (75 vs. 13%, $P < 0.001$). $HIV^-$associated nephropathy was the predominant renal diagnosis (59%) in the $HIV^+$ group. All $HIV^+$ recipients had an undetectable HIV viral load and $CD4^+$ T-cell count more than 200 cells/μl at transplantation; four (11%) and one (3%) were hepatitis B/C coinfected. Cold ischaemia time (15.0/14.8 h, $P = 0.44$) and degree of human leukocyte antigen (HLA) mismatch (1–2 mismatches: 43/48%, $P = 0.38$) were similar for $HIV^+/HIV^-$ recipients. Maintenance immunosuppression at 3 months