Original Article

Profile of HIV and multidrug-resistant tuberculosis in orphans living in orphanages in Mumbai, Maharashtra, India

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Abstract

Aims: The aim was to study the clinical profile of HIV-infected orphans living in orphanages in Mumbai, Maharashtra, India and determine the prevalence of multidrug-resistant (MDR) tuberculosis (TB) in them. **Materials and Methods:** Seventy-four HIV-infected orphans from two orphanages (orphanage A taking antiretroviral therapy [ART] as per our prescription, whereas orphanage B taking ART from an ART center) were included in the study. Detailed history and examination was carried out in each patient. CDC class prior to ART, age at presentation, CD4 count/percent, opportunistic infections (OIs) prior to and after ART, co-infections with hepatitis B virus (HBV) and hepatitis C virus, growth, ART regimes, and treatment failure were noted in each patient. **Results:** Of 18 HIV-infected children in orphanage A, boys constituted 11 (61.1%) and girls were 7 (38.9%), whereas orphanage B had all girls (n = 56). TB was the most common OI in orphanage A prior to the start of ART seen in 15 (83.3%), whereas it was seen in 18 (32.1%) in orphanage B. In contrast, TB was seen in eight (14.2%) orphans in orphanage B after the start of ART, of which two (3.5%) were MDR-TB and another two (3.5%) were suspected to have MDR-TB, whereas one (5.5%) in orphanage A had MDR-TB. Age of presentation was 4.7 ± 3.2 years for orphanage A and 12.9 ± 2.5 years for orphanage B. On ART, malnutrition was seen in one child in orphanage A as compared to nine in orphanage B. ART was started at 6.1 ± 3.1 years in orphanage A and 10.1 ± 2.8 years in orphanage B. Zidovudine, lamivudine (3TC), and nevirapine (NVP)/efavirenz (EFV) constituted the baseline ART regimen in 13 (72.1%) orphans in orphanage A, whereas stavudine (d4T) + 3TC + NVP constituted the baseline ART in 17 (30.3%) orphans in orphanage B. Three (5.3%) orphans had HBV co-infection in orphanage B. **Conclusion:** Children in orphanage A came to us at a younger age, in more advanced stage of disease, and were more malnourished. Orphanage A was started on ART earlier in life. The prevalence of TB was higher in orphanage A prior to ART. MDR-TB was seen in both orphanages, with prevalence ranging from 3.5% to 5.5%.

Key words: HIV, India, orphans

INTRODUCTION

An "orphan" is defined by the United Nations as a child who has "lost one or both parents." Worldwide, it is estimated that more than 16 million children under 18 have been orphaned by AIDS. Around 14.8 million of these children live in sub-Saharan Africa.[1] In some countries which are badly affected by the epidemic, a large percentage of all children, for example 16% of children in Zimbabwe and 12% in Botswana and Swaziland, are orphaned due to AIDS. Even with the expansion of antiretroviral treatment access, it is estimated that

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by 2015, the number of orphaned children will still be overwhelmingly high.[2] Due to the AIDS epidemic, there is an increase in the prevalence of orphanhood, with HIV-1 seroprevalence rates being higher among orphans than among nonorphans.[3]

A study conducted in Mumbai in 2008 determined that 40% of HIV-infected children were orphans.[4] However, information on HIV-infected orphans staying in orphanages is lacking. We conducted this study to determine the profile of HIV-infected children staying in two orphanages in Mumbai.

MATERIALS AND METHODS

This retrospective study was undertaken to determine the profile and health status of 74 HIV-infected orphans living in two orphanages in the city of Mumbai, Maharashtra, India, who were referred to our pediatric HIV clinic at a tertiary children's hospital in Mumbai.

Orphanage A is a one-storied building with an adjoining play area, with forty inmates, twenty of whom are boys. Of the forty children, 18 are HIV infected and are on regular follow-up at our center from 2006. All these children live together irrespective of their HIV status. The HIV-infected children procure their antiretroviral therapy (ART) and money for CD4 testing, etc., from funds raised through charity. Orphanage B is a 10 acre area with two cottages and 400 inmates, all girl children, of which 56 are HIV infected. Each child has her own bed space but lives in a dormitory system. The children are enrolled at a government ART center which provides for their ART and 6-monthly CD4 testing. These 56 HIV-infected children were also enrolled at our center for further management in July 2012. Patients who have open tuberculosis (TB) or other communicable disease such as chickenpox and measles are kept in an isolation room in both the orphanages.

All children underwent a detailed history and thorough clinical examination. All children were classified into clinical class N, A, B, and C as per the CDC classification prior to the start of ART.[5] Mode of transmission of HIV was determined by establishing mother's HIV status (vertical) if available, evaluating history of blood/blood product transfusion (transfusion related) and sexual abuse in children. Age of presentation, nutrition status (malnutrition was determined if height or weight was $<5^{th}$ centile as per Agarwal's charts[6]), gender, baseline CD4 count and percent, age of starting ART, opportunistic infections (OIs) (prior to and after ART), co-infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), and syphilis were noted. TB was diagnosed on the basis of clinical symptoms, Mantoux test, radiological features, and/or sputum smear and culture. HBV was screened by HBsAg test and hepatitis C by hepatitis C enzyme-linked immunosorbent assay. Syphilis was screened by Venereal Disease Research Laboratory test. Other investigations such as liver function tests and ultrasound abdomen were done as and when required. ART regimens, duration on first-line ART, and latest CD4 counts as well as HIV viral loads were noted. Clinical failure was recognized with the appearance or reappearance of WHO clinical Stage 3 or Stage 4 events after at least 24 weeks on ART in a treatment-adherent child. Immunological failure was recognized as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child: CD4 count of ≤200 cells/mm^3 or %CD4+ ≤10% for a child >2 years to <5 years of age and CD4 count of ≤100 cells/mm^3 for a child 5 years of age or more. Virological failure was recognized as a persistent viral load above 5000 RNA copies/ml, after at least 24 weeks on ART, in a treatment-adherent child.[7] Multidrug-resistant (MDR)-TB was diagnosed if the tissue sample showed isoniazid and rifampicin resistance on drug susceptibility testing (DST). In both orphanages, all children were screened for TB on a diagnosis of TB in other children and those with open TB or MDR TB were put in isolation.

Demographic details of all patients were added in an Excel sheet and determined in ratios and percentages.

RESULTS

In orphanage A of the 18 HIV-infected children, boys constituted 11 (61.1%) and girls constituted 7 (38.9%), whereas orphanage B constituted all girls. The clinical profiles of both orphanages are depicted in Table 1. Infections prior to starting ART seen in children in orphanage A were TB in 15 (83.3%), chicken pox in three (16.6%), herpes zoster in four (22.2%), mumps in two (11.1%), otitis media in six (33.3%), molluscum contagiosum in five (27.7%), urinary tract infection in one (5.5%), paratracheal abscess in one (5.5%), and pneumonia in one (5.5%) orphan. Infections in orphanage B prior to start of ART were TB in 18 (32.1%), chicken pox in one (1.7%), thrush in one (1.7%), herpes zoster in three (5.3%), otitis media in three (5.3%), molluscum contagiosum in four (7.1%), herpes simplex in two (3.5%), and diarrhea in one (1.7%) orphan.

OIs seen after the start of ART were TB which was MDR in one (5.5%), thrush in one (5.5%), otitis media in three (16.6%), and molluscum contagiosum in three (16.6%) children in orphanage A. In contrast, OIs seen in orphanage B after the start of ART were TB in eight (14.2%) children, of which two (3.5%) were MDR-TB and another two (3.5%) were suspected to have MDR-TB. Chicken pox, thrush, herpes zoster, warts, and diarrhea were seen in one (1.7%)

Table 1: Clinical profile of HIV-infected orphans

	Orphanage A (*n*=18) at presentation (July 2006), *n* (%)	Orphanage A (*n*=18) at last follow-up (May 2012), *n* (%)	Orphanage B (*n*=56) at presentation (July 2012), *n* (%)
Age (years)	4.7±3.2	9.83±3.12	12.95±2.5
ART prereferral	2 (11.1)	13 (72.2)	30 (53.5)
Malnutrition	11 (61.6)	4 (22.2)	14 (25)
Malnourished on ART	1	3	9
CD4 (cells/mm^3)	731±518	907±431	795±475
CDC Class (only those not on ART)			
N	0	0	11 (19.6)
A	3 (16.6)	1 (5.5)	6 (10.7)
B	11 (61.1)	2 (11.1)	9 (16.0)
C	2 (11.1)	0	0
Immune category (not on ART)			
None	9 (50)	16 (88.88)	20 (35.7)
Mild	3 (16.6)	2 (11.11)	6 (10.7)
Advanced	1 (5.5)	0	0
Severe	2 (11.1)	0	0
Unclassified	1 (5.5)		
Age at the start of ART (years)	6.1±3.1		10.1±2.8
First-line ART regimes			
AZT + 3TC + NVP	10 (55.5)		7 (12.5)
AZT + 3TC + EFV	3 (16.6)		1 (1.7)
D4T + 3TC + NVP	0		17 (30.3) of which 3 have been recently shifted to AZT instead of D4T
D4T + 3TC + EFV	2 (11.1)		1 (1.7)
D4T + 3TC + NVP shifted to AZT + 3TC + NVP as part of government program			3 (5.3)
Second-line ART		1 (5.5)	
Not on ART		3 (16.6)	26 (46.4)
Duration (years) on first-line ART	3.5±2.9		3±2
CD4 count at start of ART (cells/mm^3)	550±415		274±165.8
HBV co-infection	0	0	3 (5.3) (all had normal liver function test)
HCV co-infection	0	0	0
Syphilis	0	0	0
Immunological failure (on follow-up)	1 (5.5)		0
Virological failure (on follow-up)	2 (11.1)		-

AZT=Zidovudine; 3TC=Lamivudine; NVP=Nevirapine; D4T=Stavudine; EFV=Efavirenz; TB=Tuberculosis; MDR TB=Multidrug-resistant TB; ART=Antiretroviral therapy; HBV=Hepatitis B virus; HCV=Hepatitis C virus

child each and otitis media was seen in five (8.9%) children, whereas molluscum contagiosum and herpes simplex were seen in two (3.5%) children each. TB was detected in the girl in orphanage A after 5 years of ART, whereas the mean time to develop TB in orphanage B was 3.3 years after ART, hence suggesting that they were unlikely to be immune reconstitution syndrome and more likely to be recent infection. All patients with MDR-TB had received TB treatment in the past. There were no index adult cases of TB in both orphanages. The baseline CD4 in patients who had developed TB in orphanage B before ART was 284.2 cells/mm^3, whereas peak CD4 after the start of ART was 1145.8 cells/mm^3. The mean CD4 at the time of diagnosis of TB was 821.4 cells/mm^3. In orphanage A, baseline CD4 of the patient with TB was 117 cells/mm^3 prior to ART and CD4 count at the time of TB was 498 cells/mm^3.

Viral load testing was done in ten children in orphanage A on follow-up and none in orphanage B. Of these ten children, five (50%) had undetectable viral load.

At the first visit, 11 children from orphanage A were malnourished and only one was on ART prior to referral. Nine of the 11 malnourished children are on ART since then and five of them have achieved normal growth. One of those four has also been detected to have immunological failure as well as virological failure with inadequate growth, hence has been started on second-line ART for 5 years. Orphanage B visited us for the first time a few weeks prior to conducting this comparative study. At that time, 14 of the 56 children were malnourished. Nine of these malnourished children were already on ART. On evaluation for growth faltering, it was found that four of these 14 malnourished children

were also suffering from MDR-TB (two proven and two suspected).

There are adherence issues in both orphanages. In orphanage A, the girl on second-line ART is not compliant with her therapy and often throws her medicines out of the window. Thus, the caretaker has to give direct observed therapy. Similarly, in orphanage B, one girl has a tendency to run away from the home.

DISCUSSION

The fact that HIV-infected children are disadvantaged in terms of schooling, nutrition, and health care was also proven by the 2003 Kenya Demographic and Health Survey.[8] A study conducted by St. John's Medical College Hospital, Bengaluru, including children enrolled at an orphanage between 2008 and 2011, proved that in their study, at baseline, 79% were underweight and 72% were stunted. All children showed significant increase in weight and height irrespective of the ART status. These findings suggested that good nutrition even in the absence of ART can bring about improvement in growth, if a holistic approach to their management and care is implemented.[9] In our study, four children in orphanage A and nine children in orphanage B remained malnourished in spite of ART, suggesting that only ART may not help to build up nutrition and a complete holistic approach is required for normal growth.

A study conducted at the Ragon Institute of MGH, MIT, USA, revealed that age at initiation, protease inhibitor therapy, and TB co-infection were each independently associated with primary virological failure.[10] Comparing results with our study, that of the above-mentioned three factors, co-infection with TB did increase chances of treatment failure and growth faltering. As for younger age of initiation of ART, it has proven favorable for children of orphanage A. Treatment failure was noticed in one patient in orphanage A based on virological failure. We have not been able to do viral loads in orphanage B due to cost issues. Thus, we have not been able to pick up early treatment failure in these patients. However, the incidence of malnutrition and OI such as TB and MDR-TB was much higher in orphanage B, suggesting that virological tests may be required also in these children earlier than waiting for immunological or clinical failure.

Adolescents are developmentally at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity intersect and compete with concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and the need to "fit in" with their peers. This makes it challenging to attract and sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses such as HIV infection. HIV-infected adolescents are especially vulnerable to specific adherence problems based on their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include denial and fear of their HIV infection; misinformation; fear and lack of belief in the effectiveness of medications; low self-esteem; unstructured and chaotic lifestyles; mood disorders and other mental illness; and lack of familial and social support. Hence, decisions regarding ART regimens in adolescents are ideally individualized to each patient and should be made carefully in context with the individual's clinical status.[11] Most children from orphanage A at presentation were <5 years of age and are now approaching the adolescent age, whereas those in orphanage B are already in the adolescent age group. Thus, we are now dealing with adolescent issues in both the orphanages, especially the issues of adherence.

All children in both orphanages were on two nucleoside reverse transcriptase inhibitors and one nucleoside reverse transcriptase inhibitors regimen. Most children in orphanage A were on zidovudine (AZT)-based regimen, whereas most children in orphanage B were on stavudine (d4T)-based regimen. As d4T is now being phased out from the government program,[12] three patients on d4T in orphanage B are now being shifted to AZT. As only a single drug is being changed, it would be wiser to do a viral load testing in these patients to rule out virological failure. However, none of these children had a virological testing done to determine if they had any virological failure. Children in orphanage A were started on ART at a younger age as most were symptomatic in CDC Classes B and C and had immunosuppression. All these children are currently doing well on treatment without clinical or immunological failure except one child who is already on second-line ART. However, children in orphanage B though almost on similar years on ART and though not having immunological failure had more comorbidities as compared to those on orphanage A such as TB and MDR-TB, suggesting that viral load testing would be essential in these patients to look for virological failure.

Children in orphanage A had more infections as compared to orphanage B prior to the start of ART. The incidence of OIs decreased dramatically after ART though the incidence of otitis media remained high, probably due to younger age. However, children in orphanage B had more incidence of TB on ART, of which two were MDR-TB and two more were suspected to have MDR-TB. The probable reason for such a high incidence of TB in orphanage B could reflect the fact that overcrowding and lack of ongoing screening for TB resulted in late detection and spread of

TB among inmates, as these children were screened for TB only when they were referred to our center. In fact, both these children with MDR-TB had been on DOTS from the government center for the past 5 months without any relief, and it was only when their sputum for TB culture and DST was done, the MDR strain picked. Both children are currently on second-line anti-tuberculous therapy. In order to curb the spread of TB between inmates in orphanages, administrative control measures including prompt diagnosis, isolation, and treatment of TB patients should be done.

Similarly, active screening for HBV and HCV co-infection detected three children in orphanage B to be HBV infected, however none of them had liver dysfunction. In patients infected with HBV, HIV can lead to higher rates of chronicity, decreased rates of anti-HBe and anti-HBs seroconversion, and increased viral replication, probably due to the impairment of the body's immune responses. As a consequence, HBV/HIV co-infection is associated with increased liver fibrosis progression and increased rate of liver decompensation, cirrhosis, liver cancer, or liver failure.[13] Hence, unless these comorbidities are actively looked for in the HIV-infected orphans, they are bound to be missed, as the status of HBV and HCV in parents of these orphans is generally unknown.

CONCLUSION

HIV-infected children in orphanages are on treatment with ART for several years. However, co-infections such as TB are common. Increase in MDR-TB is also on the rise in them. Most of these orphans are now approaching adolescent age group. Treatment failure is not easily identified in them as virological monitoring is not done for all children.

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Conflicts of interest
There are no conflicts of interest.

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