ORIGINAL ARTICLE

Lessons from a seven-year experience of paediatric HIV in Pakistan: A single centre experience

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Abstract

Objective: To describe demographic, clinical and immunologic features of children with human immunodeficiency virus.

Methods: This descriptive study was conducted at the Shifa International Hospital, Islamabad, Pakistan, from 2005 to 2011, and comprised children with human immunodeficiency virus and acquired immune deficiency syndrome. Patients with detailed physical examination and appropriate investigations and those eligible for therapy were included. SPSS 21 was used for data analysis.

Results: Of the 43 patients, 27(62.8%) were boys and 16(37.2%) were girls. The overall median age was 5 years (interquartile range: 3-8.5 years). Moreover, 18(42%) children were aged equal to or below 5 years. Fathers of 5(12%) children and mothers of 6(14%) children had died. Siblings of 3(7%) patients, fathers of 20(47%) patients and mothers of 31(72%) patients had human immunodeficiency virus or acquired immune deficiency syndrome. The median duration of breastfeeding was 24 months (interquartile range: 15-24 months). Risk factors identified were foreign job by father in 12(28%) patients, birth by vaginal delivery in 20(47%), breastfeeding >6 months in 34(79%), fathers with human immunodeficiency virus or acquired immune deficiency syndrome in 20(47%), mothers with human immunodeficiency virus or acquired immune deficiency syndrome in 31(72%) and lack of maternal anti-retrovirals during pregnancy in all (100%). There were 27(63%) children being symptomatic and 29(67%) had advanced disease at diagnosis with World Health Organisation's classification stage 3 or 4.

The pretreatment median CD4 count was 294.5 cells/mm^3 (IQR, 208.5-808) and a follow-up CD4 of 757 cells/mm^3 (IQR, 352-874) which was significant ($p < 0.005$). The intial median HIV viral load was 83 RNA copies$x10^5$/mm^3 (IQR, 1.8-8.25). Anti-retroviral therapy (ARV) was initiated in 65% (28/43) with good compliance. The mean duration of follow-up was 12 months. There was clinical and immunologic improvement in 65% (18/28) in first 12 months. There were opportunistic infections in 20 children (46%), serious side effects in 5 (18%), progression of disease or poor response in 7 (16%) and discontinuation or switch of therapy in 2 (7%). Four children had suspected HIV drug resistance but confirmed in 2 (6.7%) requiring second-line therapy. Five children (12%) died, two within one week of diagnosis.

Conclusion: Most human immunodeficiency virus-infected children had risk factors, present with severe immune suppression and had improved CD-4 after anti-retroviral therapy.

Keywords: HIV, Paediatric AIDS, Antiretroviral therapy, Pakistan. (JPMA 67: 105; 2017)

Introduction

By the end of 2013, the number of people living with human immunodeficiency virus (HIV) was 35 million in the world, with 1.5 million deaths, according to the World Health Organisation (WHO).[1] Of them, an estimated 3.3 million are children, with 260,000 new cases and 210,000 deaths. Majority (91%) of children are in sub-Saharan Africa.

The general population prevalence in Pakistan is estimated to be 0.1 to <0.5%.[1] However, high-risk groups exist within the Pakistani population that maintain a 10- to 20-fold higher prevalence of HIV than the rest of the population.[2-12] The number of children with HIV across Pakistan is small, but has been rising.

The current study was planned to describe demographic, clinical and immunologic features of children with HIV and their outcome and challenges of management.

Patients and Methods

This descriptive study was conducted at the Shifa International Hospital, Islamabad, Pakistan, from 2005 to 2011, and comprised children with HIV and acquired immune deficiency syndrome (AIDS). All HIV-antibody positive children who were diagnosed or referred, had detailed history and physical examination, appropriate investigations and who received therapy were included. Investigations done in most children included urine analysis, blood count, liver function tests, creatinine, titres

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for toxoplasmosis gondii immunoglobulins (immunoglobulin G [IgG] and immunoglobulin M [IgM]), cytomegalovirus (CMV) immunoglobulins (IgG and IgM), rapid plasma reagin (RPR) for treponema pallidum infection, hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibodies. Immunologic markers for HIV included cluster of differentiation 4 percentage (CD4%) counts and HIV viral load (ribonucleic acid[RNA] copies/mm^3). Chest x-rays and other imaging studies were also done as indicated.

Therapy was initiated after immunologic and viral loads were determined as per WHO criteria.[13] A combination of the two nucleoside reverse transcriptase inhibitors (NRTI's), zidovudine (ZDV) and lamivudine (3TC), plus either the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevaripine or the protease inhibitor (PI) nelfinavir were initiated as per WHO criteria. Nearly all patients were provided free antiretroviral (ARV) therapy and laboratory evaluation through the National AIDS Control Programme (NACP), Pakistan. Regular follow-up with clinical and immunologic markers (height, weight, basic laboratory parameters, CD4 counts and HIV viral load), side effects, documented or clinical opportunistic infections (OIs) and compliance was monitored every 3-6 months. Follow-up CD4 counts were done at least once or twice a year and viral load testing was done if there was any suspected failure of therapy. HIV drug resistance testing was done in a few cases as well. Data was analysed using SPSS 21. Demographic, clinical, laboratory features and results were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) for quantitative variables (age, duration, CD4 count, viral load, etc.) and number and percentage for qualitative variables (gender, WHO category, clinical presentation, etc.). Any statistical comparison was performed using chi-square or Fisher's exact test (<5 count) for qualitative variables and Student's t-test for comparison of means. All p-values were two-sided. P<0.05 was considered significant.

Results

Of the 43 patients, 27(62.8%) were boys and 16(37.2%) were girls. The overall median age was 5 years (IQR: 3-8.5 years). Moreover, 18(42%) children were aged equal to or below 5 years. All children were from low socioeconomic group with young parents hailing from small cities in Punjab. Fathers of 5(12%) children while mothers of 6(14%) children had died. Siblings of 3(7%) patients, fathers of 20(47%) patients and mothers of 31(72%) patients had HIV or AIDS. The median duration of breastfeeding was 24 months (IQR: 15-24 months). Risk factors identified included foreign job by father in 12(28%) cases, birth by vaginal delivery in 20(47%) cases, breastfeeding (>6 months) in 34(79%) cases and lack of maternal anti-retrovirals in all cases. The disease was at stage 1 in 5(11.6%) children, stage 2 in 2(4.7%), stage 3 in 17(39.5%), stage 4 in 12(27.9%) and severe immune suppression (stage 3 and 4) in 29(67%) patients (Table-1).

Table-1: Demographic and risk factors of children with HIV.

	Median, N (%)
Total patients	43 (100)
Males	27 (63)
Median age (years)	5 (IQR, 3-8.5)
? 5 yr old	18 (42)
Father age (Median, years)	35 (IQR, 32-39.75)
Fathers deceased	5 (12)
Mothers age (Median, years)	30 (IQR, 26-35)
Mother deceased	6 (14)
Both Parents deceased	2 (5)
Sibling with HIV or AIDS	3 (7)
Duration of breastfeeding (median, months)	24 (IQR, 15-24)
Risk Factors	
Foreign job by father	12 (28)
Birth by vaginal delivery	20 (47)
Breastfeeding (>6 months)	34 (79)
Fathers HIV positive or AIDS	20 (47)
Mothers HIV positive or AIDS	31 (72)
Maternal anti-retrovirals during pregnancy	0 (0)
HIV Classification	**N (%)**
WHO Clinical Stage	
Stage 1	5 (11.6)
Stage 2	2 (4.7)
Stage 3	17 (39.5)
Stage 4	12 (27.9)
Severe immune suppression (Stage 3 and 4)	29 (67)

HIV: human immunodeficiency virus
AIDS: acquired immunodeficiency syndrome
WHO: World Health Organisation
IQR: Inter-quartile range.

Moreover, 5(11.6%) had missed diagnosis despite risk factors, long duration of illness and repeated infections compatible with immunodeficiency. They were given transfusions, multiple antibiotics and anti-tuberculosis therapy. They had extensive evaluation for immunodeficiency with findings of anaemia, lymphopenia and higher IgG immunoglobulin levels but HIV was never suspected or tested. All children had their routine vaccinations as per Expanded Programme for Immunisation (EPI) including the live vaccines (polio and Bacillus Calmette-Guérin[BCG]) with no evidence of any serious side effects.

Initial laboratory investigations (not shown) included mean haemoglobin 9.4±2.8 g/dL, white cell count 10.8x10^3/L, mildly raised alanine aminotransferase (in

Table-2: Clinical, laboratory, radiologic and immunologic features.

	Median, IQR, N (%)
Clinical	
Duration of illness (median, months)	12 (IQR, 4-20.5)
Symptomatic	27 (63)
Failure to thrive	30 (70)
Persistent diarrhoea	29 (67)
Lymphadenopathy	28 (65)
Pallor	25 (58)
Anorexia	24 (56)
Wt loss	22 (51)
Rash	16 (37)
Cough	14 (32)
Fever	11 (26)
PCP pneumonia	4 (9.3)
CD4 count cells/mm3	
Total (N=29, median)	343 (IQR, 114.5-957)
Pre-treatment (N=10, median)	294.5 (IQR, 208.5-808)
Follow-up CD4 (N=15, median)	757 (IQR, 352-874)*
HIV RNA copiesx10^5/mm3 (N=8, median)	1.83 (IQR,1.8-8.25)

(*p<0.005)
CD4: CD4+ T-lymphocyte,
HIV: human immunodeficiency virus
PCP: pneumocystis jiroveci pneumonia (previously pneumocystis carinii pneumonia), RNA: ribonucleic acid
CD4: Cluster of differentiation 4
IQR: Inter-quartile range

Table-3: Therapy and outcome.

	N (%)
Antiretroviral therapy	28 (65)
Drugs used	
ZDV+3TC+NVP	18 (64)
ZDV+3TC+EFV	6 (22)
ZDV+3TC+NFV	4 (14)
Median duration of therapy	9 (IQR, 1.5-18.5)
Improved within 12 months	18 (65)
Total OIs	20 (46)
Serious side effects	5 (18)
Progression of disease	7 (16)
Discontinuation of therapy	2 (7)
Confirmed drug resistance	2 (7)
Median duration of follow-up	9.5 (IQR, 1.3-23.8)
Expired	5 (12)

ZDV: zidovudine
EFV: efavirenz
3TC: lamivudine
NVP: nevirapine
NFV: nelfinavir
OIs: opportunistic infections
IQR: Inter-quartile range.

7(16.3%) children), positive hepatitis B surface antigen (in 3(7%) children), giardiasis (in 1(2.3%) child), abnormal chest x-ray findings in 11(25.6%) children (pneumonia 5(11.6%), consistent with pneumocystis jerovici (PCP) pneumonia 4(9.3%), hilaradenopathy 3(7%), non-specific infiltrates 2(4.7%), empyema 1(2.3%)). Serologic tests for toxoplasmosis gondii immunoglobulins (IgG and IgM), RPR and CMV immunoglobulins (IgG and IgM) were negative for active infection in most children. All of the children were counselled for nutritional, iron and vitamin supplements, given additional vaccines including pneumococcal conjugate, haemophilus influenzae type B, hepatitis A and typhoid vaccines and co-trimoxazole for PCP prophylaxis. The overall median CD4 count was 343 cells/mm^3 (IQR: 114.5-957) during the initial evaluation (Table-2).

Anti-retroviral therapy was initiated in 28(65%) children initially as per WHO criteria 2006 guidelines and later using the updated 2010 guidelines with good compliance in majority. Depending on age, availability and as per WHO recommendations at the time of diagnosis, a combination of the two NRTIs (ZDV and 3TC) plus either NNRTI (nevaripine) or the PI (nelfinavir) was used to initiate therapy. The initial drugs used included a combination (3TC in 25(58.1%), ZDV 24(55.8%), nevirapine (NVP) 18(41.9%), efavirenz (EFV) 6(13.9%), nelfinavir (NFV) 3(6.9%) and stavudine, d4T in 4(9.3%) children). The most common drug combinations used were ZDV+3TC plus NVP (in 18(41.9%) children) or EFV (in 6(13.9%) children). Second line drugs (lopinavir/ritonavir and tenofovir or didanosine) were used in 3(7%) children and despite some intolerability had improvement clinically and in CD4 counts in 2(4.7%) children (Table-3).

In children who had initiation of ARV therapy, there was clinical and immunologic improvement in 18(65%) in the first 12 months. Moreover, the pre-treatment median CD4 count was 294.5 cells/mm^3 (IQR: 208.5-808) with improved follow-up CD4 of 757 cells/mm^3 (IQR: 352-874), which was significant (p<0.005). The mean duration of follow-up was 12.1months (±12.4) with 3.8 average visits (±3.7) per child. There were a total of 20 OIs in 13(46%) children, including recurrent skin infections (in 6(13.9%) children), tuberculosis (TB) 5(11.6%), candidiasis 4(9.3%), pneumonias 4(9.3%), gastroenteritis 3(7%), lymphoid interstitial pneumonia (LIP)2(4.7%) and septic arthritis in 1(2.3%) child.

Moreover, 7(16.3%) children had suspected HIV drug resistance but was confirmed in 2(7%) only and that required second-line ARVs. Besides,1(2.3%) 7-year-old boy who was on 3TC, ZDV and NVP since 4 years (initially given nelfinavir for 1 year) and also completed therapy for TB. He showed good response initially with CD4 count of 374 cells/mm^3 improving to 1,046 cells/mm^3 in three years.

However, his HIV RNA remained high ($1.32x10^5$ and $2.95x10^4$) on two occasions. Suspecting drug resistance, his genotyping for drug resistance was done which showed a recent viral load of 3x104 copies/ml. PI mutations detected were L90M, L10F, NRTI mutations included M41L, A62V, M184V, D67N, L210W, T215Y and K219N and NNRTI mutations were K101Q and Y181I. These mutation genes were shown with high-level reduced susceptibility or virological response.

The second child was a 5-year-old girl whose mother had shown good improvement on her ARVs (d4T, NVP and 3TC). This child had initial improvement on her anti-retrovirals (3TC, d4T, efavirenz) with a rise in CD4 from initial 262 cells/mm^3 to 780 cells/mm^3 and successfully completing TB therapy. But after more than one year had a decline clinically and her viral load climbed from $6.3x10^3$ RNA copies/ml to $4.8x10^4$ RNA copies/ml over a 6 weeks' period. The genotyping for drug resistance showed no PI mutations, but reverse transcriptase (RT) mutations included K103N, V179E, M184V and T2151T. After second line ARV therapy she had undetectable viral load over one year but then had increasing viral load that was attributed to poor compliance.

Serious side effects were noted in 5(18%) patients, and included severe anaemia in 3(7%), thrombocytopenia 1(2.3%) and drug intolerance 1(2.3%). During therapy there was progression of disease or clinical failure in 7(16%) children. Change of ARV drugs due to serious side effects and proven or potential drug resistance was done as required in 6(14%) children. Of the 5(12%) children who died, 3(7%) died after at least 6 months of therapy with evidence of clinical, immunologic or virologic failure, whereas 2(4.7%) children (aged 6 and 10.5 years) died within one week of diagnosis. Both were orphans, had advanced HIV, missed or late diagnosis and had very low CD4 counts (2 and 4 cells/mm^3, respectively).

Discussion

HIV is the most common cause of AIDS in children. The estimated paediatric cases account for only 4% of total HIV cases but contribute to 20% to overall mortality.[1] The first case of HIV in Pakistan was diagnosed in 1987.[5,6] Until recently, Pakistan has managed to remain classified as 'low prevalence high risk' country for HIV infection and AIDS.[7] However, this has changed and the country is in a 'concentrated phase' of the epidemic with HIV prevalence of more than 5% among injecting drug users (IDUs) in major cities.

Studies in the last three decades have shown that there are groups within the Pakistani population that through high-risk behaviour act as a potential reservoir for HIV, and that these high-risk groups maintain a considerably higher prevalence of HIV than the rest of the population.[2] The results from the 4th round of Integrated Behaviour and Biological Survey 2011-2012 in four key high-risk population [people who inject drugs (PWIDs), male sex workers (MSWs), hijra sex workers (HSWs), and female sex workers (FSWs)] in 20 Pakistani cities was done by National AIDS Control Programme and the Canadian International Development Agency.[3] It found highest HIV sero-prevalence among PWIDs at 37.8%, followed by a prevalence of 7.2% among HSWs, 3.1% among MSWs and 0.8% for FSWs.[3] Other studies have similarly documented: high incidence (12.4 per 100 person-years) among PWID,[4] different social and demographic determinants of HIV sero-conversion,[5] increasing prevalence among IDUs in 10 cities (from 16.2% in 2006 to 31.0% in 2011),[6] risky behaviours among FSWs,[7] vulnerable groups such as hijra (transgender) HSWs,[8] migrant workers,[9] intermixing between the IDUs and men who have sex with men(MSMs) populations,[10] outbreaks,[11,12] and more recently children.[14]

Experiences in Pakistani children with HIV and/or AIDS are little.[14] The presentation of HIV infection in children is similar to other illnesses common in developing countries.[15] Although no in-depth risk factors were explored, overseas employment, poor socio-economic status, breastfeeding and no maternal ARV were documented in this study that are also main barriers for health-care prevention and provision.[10-12,14,15-18]

Any child with an illness compatible with HIV infection should be properly evaluated irrespective of HIV exposure. These include neonates, infants and children with perinatal exposure, those with specific signs and symptoms suggestive of HIV infection, chronic or unexplained illness or known exposure during childhood. Differential diagnosis should include the more common childhood infections or illnesses such as severe pneumonia, malaria, gastroenteritis, typhoid, parasitic infections and tuberculosis. However, there are many clinical signs or conditions that are quite specific to HIV infection, which should be strongly suspected if these conditions are present such as PCP pneumonia, oesophageal candidiasis, LIP and Kaposi's sarcoma.[19,20] Some other features may indicate possible HIV infection such as recurrent infection, prolong oral thrush after the neonatal period, chronic parotitis, generalised lymphadenopathy, chronic haepatomegaly, progressive neurological impairment, etc. Our study had a large number of children who had prolonged and recurrent infections pointing to HIV infection and could have been

diagnosed earlier.

All children in this study presented symptomatically and had severe immunosuppression, with low CD4 counts, suffering from recurrent infections and with failure to thrive. Studies of children in resource-poor countries have similar experiences such as Pakistan,[14] India[15] and Kenya.[16] OIs are now significantly reduced due to antiretroviral therapy but continue to be one of the most common causes of morbidity in HIV-infected children in resource-poor countries, as also seen in our cohort.[17]

Over the last few years, evidence suggested to initiate ARV in children early with improved survival, lower morbidity, and improved laboratory parameters.[18,21,22] This is in part due to rapid HIV disease progression and less predictive laboratory-monitoring parameters. Current treatment guidelines by the WHO now include recommendations for earlier initiation of ARV initiation criteria from a CD4% threshold of ≤15% in 2006 to ≤25% in 2010 and include all children aged under 24 months rather than under 12 months.[21] The current preferred first-line antiretroviral therapy(ART) regimens include two NRTIs with either a NNRTI or a PI/r. For resource-limited settings, NNRTI is preferred over PI due to its lower cost by the WHO and adopted by national programmes in most countries. The second-line regimens are less accessible owing to limited paediatric formulations and availability of safe and effective drugs for children.

With the introduction of these newer ARV drugs and regimens there has been a dramatic improvement in survival and quality of life in children with HIV/AIDS even in resource-poor countries.[17,18,22-26] The response to ARV has been promising with respect to clinical, immunologic and virologic recovery, incidence of OIs, improved quality of life and mortality.[17,18,26-31] These studies have also shown that in resource-constrained countries it is possible to achieve comparable results but challenges exist that need to be overcome.[14,18,29] However, our study showed that approximately two-thirds of children presented with WHO stage 3 or 4 disease associated with poor outcome but two-thirds improved after ARV therapy with significant increase in CD4 within one year. HIV viral load and drug resistant testing was seldom used in our cohort owing to logistical and financial considerations. Also, about half had some documented OI and about one-fifth had serious side effects. Mortality was 12% which is higher than in other reports from Asian countries.[18]

According to the NACP, the estimated number of total HIV-infected patients in Pakistan is 96,000.[32] Out of the total 15,668 registered cases, 7,356(46.9%) are on ARV therapy. Out of the total 496 registered paediatric cases, 162(33.7%) children are getting ARVs. In our cohort, a large number (65%) of children were on ARVs. For children with HIV in Pakistan the challenges with identifying, diagnosis, initiating and maintaining complicated and accurate ARV regimens are numerous despite the nationwide establishment of HIV treatment and care centres by the NACP. The issues are diverse such as early identification, availability of drugs, particularly paediatric formulations, second-line drugs impacting compliance and lack of expertise in care of such children.[13] The lack of parental education, poor socio-economic means and a poor health infrastructure are inhibitory to regular follow-up which is essential for such patients. This can be partially overcome by maintaining linkages and excellent parent-clinician relations, providing strong encouragement and stressing the importance of the follow-up visits.

Conclusion

Most HIV-infected children had risk factors, present with severe immune suppression and had improved CD4 after ARV therapy. Most of the children presented with advanced HIV. Clinical, immunologic and virologic recovery does occur, but maintaining HIV control in a resource-poor country may be fraught with many challenges.

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