Estimating the burden of Paediatric HIV in an 'A' category district in India: An epidemiological study

Anju Sinha (apradhandr@gmail.com)
Indian Council of Medical Research, New Delhi
Reynold Washington
St John's Research Institute, Bangalore
Rajeev Sethumadhvan
Karnataka Health Promotion Trust, Belgaum
Rajaram Potty
St John's Research Institute, Bangalore
Shajy Isac
Karnataka Health Promotion Trust, Belgaum
Vasantha Thavraj
Indian Council of Medical Research, New Delhi
Ravindra Pandey
All India Institute of Medical Sciences, New Delhi

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Abstract

Background: Epidemiological information on the disease burden of paediatric HIV is lacking in India. The National AIDS Control Program (NACP) provides estimates of paediatric HIV based on its projections of adult infections. The window of opportunity for diagnosis and treatment is very narrow a third of HIV infected children do not see their first birthday and half of them do not reach their second birthday. Early detection of pediatric HIV is crucial for prevention of morbidities, growth delays and death.

Methods: The study aimed to estimate the disease burden of pediatric HIV among children in 'A' category district of a high HIV prevalence state.

The study used an innovative multipronged methodology to estimate the disease burden in a high burden district in India. Details of methodology have been published and include early case detection in infants (0-18 months) born to HIV positive women, among children in families with HIV positive parents, and among sick children (0 to 14 years) presenting in a health facility and screened using a modified IMCI-HIV algorithm, were methods used. The overall burden of paediatric HIV was calculated as a product of cases detected in each strategy multiplied by a net inflation factor for each strategy.

Results: The existing pool of HIV infection in the district works out to be 3266 HIV positive children <15 years of age, among a mid-year (2013) projected child population of 1401688, thus giving us an overall HIV prevalence among children of 0.23%. The proportion of children among all people living with HIV in the district works out to 10.4% (3266/ (3266+28119)

Conclusions: The study reported a higher prevalence than reported earlier from projections of the NACP. An overall 0.23% HIV prevalence among children was estimated which is 2.5 times that of the earlier reported prevalence for Karnataka state. The proportion of children among all persons living with HIV in Belgaum district in this study is 10.4% against 6.54% reported earlier for India. The study methodology is replicable for other settings and other diseases.

Introduction

Globally the population of People living with HIV is on the rise and projected as a threat to public health. Countries are not on track for the UNAIDS 2020 and SDG 2030 targets[1]. It is estimated that 1.94 million children will be living with HIV in 2020[2]. There are few estimates of the magnitude of Paediatric HIV. Mathematical modeling based estimates using the Spectrum and Estimation and Projection Package (EPP) model cover only 15–45 year old population[3,4]. In India, a country with 1.3 billion people, children up to 18 years constitute 41% of the total population[5], but lacks accurate estimates of the pediatric HIV burden. This is needed to save and improve lives of HIV exposed children. The National AIDS Control Program provides estimates of Paediatric HIV that are based on its proportion to adult infections, but uses available data from other countries, in order to arrive at this estimate[6]. The WHO recommended various methods to estimate Paediatric HIV including case reporting, household surveys, immunization clinic surveys, in-school and out-of-school surveys, mortality data and vital registration. These have been used in countries with a

high HIV prevalence: South Africa, Nigeria, Kenya, Thailand, Argentina, Mozambique, Malawi, Indonesia and others[7, 8]. Similarly, the WHO and UNAIDS recommended measurement of HIV prevalence among children (0–14 years) in settings where the HIV prevalence among women in the reproductive age is 5% or greater, with high fertility rates, low coverage of prevention of mother to child transmission (PMTCT) services and where resources to conduct a large sample survey among children is feasible. India's low overall adult HIV prevalence and limited resources for large scale surveys do not meet these criteria and hence Paediatric HIV measurement is excluded in many large scale surveys partly due to limitation of sample sizes for a robust pediatric burden measure[3]. India therefore lacks direct Paediatric population level data that can help the country arrive at more accurate estimates of the magnitude of Paediatric HIV.

One of the goals of the National Strategic Plan to end AIDS (2017–2024) is the elimination of mother to child transmission (EMTCT) of HIV. Mother to child transmission (MTCT) remains the main reason for HIV infection among children in India. Despite the availability of tools and methods to prevent, identify and treat HIV in children, India's performance on this front has lacked lustre. By 2020, 95% of pregnant women should have received testing for HIV and syphilis and 95% of estimated positive pregnant women should be on antiretroviral treatment (ART) in order to achieve an MTCT of less than 5%. However, by 2015, India had registered only 74.2% of 29.7 million pregnancies during the antenatal period and only 59% of these were tested for HIV. Only 45% of an estimated 35,255 HIV positive pregnant women received ARV. Out of 10,677 HIV positive live births, 85% of babies were tested at least once in 2016-17, but only 59% were tested within two months. The lack of technology enabled platforms and inadequate utilization of front-line workers for this purpose, results in a linkage loss at every level[9]. The 'start free, stay free and AIDS free' platform offers India an opportunity for focused, coordinated action and renewed commitments to end Paediatric AIDS and to eliminate MTCT[10]. In the absence of ART, approximately 30% of untreated HIV-infected children die before their first birthday and more than 50% die before they reach 2 years of age[11]. With early diagnosis and early initiation of treatment, survival improves substantially with only 20% of babies dying by their first birthday[12]. Untreated HIV infection in children results in growth delays that may not be reversed by ART[13]. It is therefore crucial to have reliable estimates of Paediatric HIV, in order to plan, implement and monitor the coverage of prevention and control efforts in HIV infected children.

The Indian Council of Medical Research commissioned a task force study to estimate the burden of Paediatric HIV in a category 'A' district of a high prevalence state. The study protocol has already been published previously[8].

Methods

Aim and study design: The aim of the study was to estimate the disease burden of pediatric HIV among children in 'A' category district of a high HIV prevalence state, using a multipronged approach

Study setting: The study comprised of three distinct strategies including active surveillance, inclusion of public and private healthcare facilities, data collection from blood banks and NGOs and children attending general and specialized clinics for a better estimation of Pediatric burden. Information regarding study

setting and design and sample size estimation have been previously described[14]. Briefly, District Belgaum was selected after a baseline assessment of three high prevalence districts in South India. Belgaum was chosen for the study as it had a high adult HIV prevalence of 1.43% in 2011[15]. Besides, the coverage of antenatal care and prevention of mother to child transmission (PMTCT) services was high and the district administration was supportive of the study. A mapping of all 971existing (Govt. & private) health care facilities (HCFs) in the district was conducted (ref published report). A total of 285 HCFs from ten talukas with stand-alone and reporting HIV testing facilities (149 Govt. and 136 private) were included in the study.

In 2011, Belgaum district had a total population of 4779661 (Males: 50.7%, Females: 49.3%), 75% of whom were rural and 73.5% (Males: 82.2%; Females: 64.6%) were literate. **Strategy 1** used a prospective cohort design to measure the incidence rate of HIV by early case detection in infants and young children (0-22 months) born to a HIV positive pregnant woman registered at one of the public or private health care facilities of the district. The study team visited the identified HCF twice in a week. A crude line list was prepared from the secondary data collected from the HCFs, the list was refined by applying eligibility and removing duplicates. All HIV infected pregnant women residing in any of the 10 talukas, who consented for age –specific HIV blood test for their infants were eligible for enrolment. The women were contacted over phone and visited physically at home or elsewhere (if home visit was not permitted). Pregnant women were followed through their pregnancy & delivery, visited once in a month until delivery and afterwards till their infant was 22 months old. A mother and infant form was filled for each mother- infant dyad. Age-appropriate early testing in infants using DNA PCR dry blood spot (DBS) was conducted at 6-10 weeks, 6-9 months and antibody based ELISA tests at 18-22 months. Demographic information, mother –infant form and a pregnant Positive Women line-list was maintained. Each mother and infant Dyad was assigned a unique identification number.

Strategies II and III used a cross-sectional design. Strategy II aimed to detect HIV infection among children (0-14 years) by family screening of HIV positive parent(s) (PLHAs) referred from ICTC centers, blood banks and community based NGOs in all 10 talukas. If a positive male was detected his wife and children were tested, if a positive female was detected her husband and children were tested. Any HIV infected man/woman, of age 18-49 years, having a biological child of 0-14 years residing in any taluka of Belgaum, who consented for testing of their spouse and children for HIV were eligible and included in strategy II of the study. Public and private HCFs were visited twice a week by the designated teams to check information about HIV infected individuals 18-49 years, they were contacted to find if they had any biological children 0-14 years. The spouse and all children of the positive person (male or female) were subjected to age appropriate HIV testing. Demographic details, data on testing were recorded. A unique identification number for the positive persons identified through family screening was created. The strategy III used screening of sick children visiting health care facilities, in four talukas of Belgaum that included 10 Health care facilities selected using stratified random sampling on the basis of MTCT prevalence, government and non-government, and by levels of health care offered. IMCI -HIV criteria (applicable to 0-5 years age) was adapted by Indian experts to include children >5 to 14 years into the algorithm. Sick children (0-14 years) presenting with suspected signs and symptoms satisfying the 'Modified Integrated Algorithm' (including sign symptoms from the IAMI and 'special clues') [16] were tested at health care facilities by age appropriate

HIV tests. Health care providers from the four participating talukas were trained in the use of the algorithm, operational definitions were developed for each criteria included in the algorithm. The facilities were visited weekly by the research team to find information about children screened positive, referred & tested. Tracking for test results was done through the unique identification number maintaining confidentiality. The strategies (I, II, & III) were expected to comb the district with pediatric cases hidden within families and presenting as masked sicknesses yet unidentified as HIV)

Estimates derived from each of the strategies (1, II & III) were multiplied by an inflation factor derived in a workshop of investigators and the Project Advisory Group/subject experts. The results from the study were extrapolated to the population characteristics within the district, including total population (adult and child), estimated overall adult HIV prevalence, estimated prevalence among pregnant women and reported coverage of HIV testing among the antenatal sub-population. The outline of the study design is depicted in Figure 1.

Figure 1: Outline of the research study

The ethics approval for the study was obtained from the Institutional Ethics Committee of St. John's Medical College, Bangalore, and regulatory approvals were obtained from NACO, the Karnataka State AIDS Prevention Society (KSAPS) and District AIDS Prevention and Control Unit (DAPCU, Belgaum district.

Study implementation: The ten talukas in the district were divided into three clusters, each of which had five Field Investigators (FIs) and a supervisor (Senior Research Fellow, SRF). In each cluster, a team of one male and one female FI was given charge of two talukas each (strategy 1 & 2), and one additional FI was allotted for the strategy 3 related work. 14 FIs were recruited and trained over two periods, for a total duration of 10 days in technical skills as well as soft skills of maintaining confidentiality& gender sensitive approach. The overall field study was supervised by a medically qualified professional. SRFs planned daily visits of FIs, validated 5% of data and verified forms for accuracy and completion.

Data Management & statistical analysis: Data was double entered using Microsoft Access, cleaned and verified for consistency and analyzed using SPSS version 22.0 and STATA version 13.0

A Project Advisory Group (PAG) guided the study team to develop a Statistical Analysis Plan (SAP). The primary outcome in strategy 1 was cumulative incidence, calculated as the number of new infections per total number of children at risk. A child was at risk till first positive result by any test at any age, by age appropriate testing. For censored observations, time was the duration of follow up. The SAP considered the limitations in coverage of services and response rates, and guided to determine the 'Net inflation factor' for each of the 3 strategies. Under strategy I the net inflation factor was derived using the estimated number of pregnancies in the district, proportion of un-tested pregnancies, pregnant mothers not enrolled and un-tested children.. In strategy II and III prevalence of HIV infection among children 0-14 years of age was calculated. Data was analyzed as per the SAP. It was based on the actual/projected 18-49 year population in the study period, estimated number of 0-14 year children, proportion of eligible index persons not recruited and not proportion of eligible children not tested. In strategy III the factors considered for Net Inflation factor were: actual/projected 0–14 year population during the study period, estimated number of

0–14 year children experiencing any morbidity, estimated morbid children reaching a HCF for care, estimated children satisfying screening algorithm, and suitable inflation factors for geographical and institutional factors, morbid children not reaching selected HCF but reaching other facilities in the district, un-screened, non-enrolled and untested children. The estimates derived under the strategies were then multiplied with the inflation factor to come up with the overall estimate. The steps followed are described along with the results section.

Results

In Strategy 1, we line listed 750 HIV infected pregnant women from 285 selected health care facilities. After exclusion of duplicates, those resident/had moved outside the district, died or who were no longer pregnant, we recruited 469 HIV infected mothers who had delivered between 2011 and 2013, and who consented to participate in the cohort study. Twenty-seven mothers had a repeat pregnancy during the study period. Thus the total number of pregnancies was 496. Among the 496 pregnancies, 477 (96%) resulted in live births, 10 (2%) in abortions and 9 (2%) in still births. Among the live births, 10 were twin pregnancies. Thus, the total number of live born babies was 487. Of 487 HIV exposed live born children, 454 (92.3%) children were tested at least once, and 39 were found to be HIV positive during follow up by 22 months of age. The net cumulative incidence rates of vertical transmission of HIV per 100 pregnancies were 2.1, 5.3 and 7.8 at 0–10 weeks, 0–9 months and 0–22 months of age, respectively. The annual cumulative incidence rate (%) was calculated to be 5.32%.

In order to calculate the inflation factor at a population level, the following indicators as per the flow diagram (Fig. 2) were conceptualized. The basic parameters were taken from the Census data (Table 1). Based on this, the indicators in the flow diagram were deduced as in the Table 2. Based on this inflation factor, the occurrence of new Paediatric HIV infections from MTCT is 41.2 (rounded off to 41) children by the age of 22 months.

Figure 2

Conceptual diagram for calculating inflation factors and burden of Paediatric HIV from Strategy 1.

Table 1
Census data for Belgaum district, 2011, considered for calculating inflation factors and burden of Paediatric HIV, Strategy 1.

Sl. No.	Parameter	Total	Male	Female
1	Population, Belgaum district, 2001	4207264	2147746	2059518
2	Population, Belgaum district, 2011	4779661	2423063	2356598
3	Annual Growth Rate	0.012756	0.012061	0.013475
4	Projected population, Belgaum district, April 2012 (Mid-study year population)	4841019	2452465	2388567
5	Proportion of 15–49 years population, 2011	0.534365	0.536863	0.531796
6	Crude Birth Rate, Belgaum district, 2011 (Source: CRS, 2011)	19.71		
7	Estimated pregnancies, Belgaum district, 2012	95416		

Table 2
Calculation of inflation factors for Strategy 1

Sl. No.	Indicators in the Flow chart for Strategy 1	Number
8	No. of pregnant women tested (Source: PPTCT data, Belgaum district, 2012)	90070
9	No. of pregnant women not tested (=(7)-(8))	5346
10	No. of HIV positive pregnant women among tested (Source: PPTCT data, Belgaum district, 2012)	187
11	HIV positivity among pregnant women (=(10)/(8))	0.002076
12	No. of HIV positive pregnant women among those not tested (=(11)*(9))	11
13	Total no. of HIV positive pregnant women in the district, 2012 (=(10)+(12))	198
14	Total no. of HIV positive pregnant women in the district during the study period (29 months)	479
15	No. of HIV positive mother-child pairs enrolled in the study	506
16	No. of enrolled HIV pregnant women whose child was tested	454
17	Inflation factor (=[(15)/(16)]*[(14)/(15)])	1.0551

In Strategy 2, we initially recruited 563 households from 671 eligible for recruitment, with 1062 children (Male: 565; Female: 497), after eliminating duplication, those not resident or who had migrated from the district, those who could not be contacted. 206 households from strategy 1, who had children from previous pregnancies, were also included in this sample. Thus, in the 769 Households with 1388 children of age < 15 years, 1241 (90.1%) were tested for HIV. 131 tested HIV positive, giving a HIV prevalence of 10.6%. (Males:

12.8%; Females: 8.4%). The HIV prevalence was 18.6% (M: 23%, F:13%) in the < 5 year age group and 8% (M:9.2, F:6.9%) in the 5–14 year group. In order to project these findings for the district population, we used the following criteria as shown in Fig. 3.

Figure 3

Conceptual diagram for calculating inflation factors and burden of Paediatric HIV from Strategy 2.

For this, the basic parameters required are taken from the Census data available (Table 3). For estimation of PLHIV in the district of Belgaum, the following calculation was adopted (Table 4). Based on this, the indicators in the flow diagram (inflation factors) were deduced (Table 5).

Table 3
Census data for Belgaum district, 2011, considered for calculating inflation factors and burden of Paediatric HIV, Strategy 1 & 2.

Sl. No.	Parameter	Total
1	Projected population, Belgaum district, Feb 2012 (Mid study population) (From table 19 above)	4841019
2	Proportion of 15–49 years population, Belgaum district, 2011	0.534365
3	Proportion of 18–49 years population, 2011	0.478696
4	Projected 15–49 years population, Belgaum district, Feb 2012	2586871
5	Projected adult 18–49 years population, Belgaum district, Feb 2012	2317376
6	No. of children of age 0–14 years, Belgaum district, 2011	1366381
7	Projected children population (0–14 years), Belgaum district, Feb 2012	1383922
8	Child/Adult ratio, Belgaum district, Feb 2012	0.597193

Table 4
PLHIV estimation*, Belgaum district.

Sl. No.	Parameter		Number
9	Sex ratio (Source: Census data, 2011)		960
10	Percentage of men having high risk sexual activity		6.0
11	Estimated FSWs		11766
12	Estimated MSM T		2333
13	Estimated IDUs		37
14	Estimated clients (=(1)*[1000/(1000+(9))]*((10)/100)		79190
15	Total high risk population (=(11)+(12)+(13)+(14))		93326
16	Remaining 15–49 years population (=(7)-(15))		2493545
17	HIV prevalence, FSW	Min	16.40
18		Max	27.34
19	HIV prevalence, MSM	Min	5.51
20		Max	10.62
21	HIV prevalence, IDU	Min	2
22		Max	2
23	HIV prevalence, Clients	Min	3.85
24		Max	8.55
25	HIV prevalence, ANC	Min	0.69
26		Max	0.95
27	Adjusted HIV prevalence, ANC	Min	0.69
28		Max	0.95
29	Number of HIV positive FSWs	Min (=(11)*(17)/100)	1930
30		Max (=(11)*(18)/100)	3217
31	Number of HIV positive MSM	Min (=(12)*(19)/100)	129
32		Max (=(12)*(20)/100)	248
33	Number of HIV positive IDUs	Min (=(13)*(21)/100)	1
34		Max (=(13)*(22)/100)	1

*Sl. Nos. 10–13, 17–26: Source: Estimation of HRGs, Technical Report, NACO, 2009.

Sl. No.	Parameter		Number
35	Number of HIV positive Clients	Min (=(14)*(23)/100)	3049
36		Max (=(14)*(24)/100)	6771
37	Number of HIV positive general population	Min (=(16)*(27)/100)	17205
38		Max (=(16)*(28)/100)	23689
39	Total Number of HIV positive in the district	Min (=(29)+(31)+(33)+(35)+(37))	22313
40		Max (=(30)+(32)+(34)+(36)+(38))	33925
41	Average Total PLHIV 18–49 years, Belgaum district (=(39)+(40)/2)		28119
*Sl. Nos. 10–13, 17–26: Source: Estimation of HRGs, Technical Report, NACO, 2009.			

Table 5
Calculation of inflation factors for Strategy 1 & 2.

Sl. No.	Indicators in the Flow chart for Household information analysis	Number
42	Estimated 18–49 year HIV positive adult having a child of age 0–14 years (=(41)*(8)).	16792
43	No. of 18–49 year HIV positive adult having a child of age 0–14 years enrolled	769
44	No. of 18–49 year HIV positive adult having a child of age 0–14 years not enrolled (=(42)-(43)).	16023
45	No. of children 0–14 years of age for enrolled adults.	1388
46	Average no. of children per enrolled adult (=(45)/(43)).	1.805
47	Expecting same proportion of children for adults not enrolled, No. of children 0–14 years of age for adults not enrolled (=(46)*(44)).	28921
48	Total No. of children 0–14 years of age for 18–49 year HIV positive adult in the district (=(45)+(47)).	30309
49	No. of children 0–14 years of age (for enrolled adults) tested in the study.	1241
50	No. of children 0–14 years of age (for enrolled adults) not tested (=(45)-(49))	147
51	No. of children 0–14 years of age for enrolled adults tested positive in the study	131
52	HIV positivity among the tested children (=(51)/(49)).	0.10556
53	Expecting same proportion of HIV positivity among children not tested, No. of HIV positive 0–14 years children among untested children (=(52)*(50)).	16
54	Total No. of 0–14 years HIV positive children for enrolled 18–49 year HIV positive adult (=(51)+(53)).	147
55	Estimated children (0–14 years) HIV positive in the district (=(48)*(52)).	3199

In strategy 3, of the total 33342 children who visited the 10 health care facilities during the study period, 24342 (73%) were screened by the trained field investigators. 527 (2.2%) sick children were identified, 509 completed HIV testing requirements. Of these, 97 children turned out to be positive (HIV prevalence 19.1%), but 86 of them had prior knowledge of their HIV positive status. The study was therefore able to identify 11 (2.16%) new HIV infections from among the total 509 sick children. For strategy 3, it was assumed that HIV infection would be nil among the 23815 screened children who did not have any indicative symptoms or social risk criteria for HIV and AIDS. The parameters considered are given in Table 6.

Table 6
Calculation of inflation factors for Strategy 3

Sl. No.	Parameter	Total
1	Population, Belgaum district, 2001	4207264
2	Population, Belgaum district, 2011	4779661
3	Annual Growth Rate	0.012756
4	Projected population, Belgaum district, 2014	4966110
5	Proportion of 0–14 years population, Belgaum district, 2014	0.285874
6	Estimated 0–14 year population, Belgaum district, 2014	1419682
7	Assuming 10% of children as morbid, estimated no. of children experiencing any morbidity in the district in a year	141968
8	Assuming 70% of these morbidities/clinic visits are unique children, expected no. of unique morbid children in the district in a year (=(7)*0.7	99378
9	During the study period (127 days), total no. of children reached at HCFs for any morbidity	33342
10	During the study period (127 days), no. of children screened at HCFs (127 days)	24342
11	Assuming 70% of these morbidities/clinic visits are unique children, expected no. of unique morbid children in the district in a year (=(10)*0.7	17039
12	No. of children not screened (even if they reached at HCF in 127 days + had the screening been done for remaining 238 days in a year) (=(8)-(10))	82339
13	No. of children screened positive (sick children) and enrolled in the study	527
14	No. of unique children screened positive (sick children) and enrolled in the study	515
15	No. of enrolled sick children tested for HIV in the study	509
16	No. of unique enrolled sick children tested for HIV in the study	497
17	No. of tested sick children found positive in the study	97
18	No. of unique tested sick children found positive in the study	89
19	No. of unique newly detected unique HIV positive children among (18)	11
20	Percent of new unique positive children identified among all unique screened positive (sick children) (=(19)/(16))	2.2
21	If all children were tested, new positive children that could be identified from the study (=(14)*(20))	11.40
22	Estimated unique children who would have been identified as sick among the unscreened (=[(14)/(11)]*(12))	2488.7
23	Estimated no. of unique positive children among the unscreened (=(20)*(22))	55.1

Sl. No.	Parameter	Total
24	Total new unique positive children that in the district in a year (=(23)+(21))	67

Estimating the burden of HIV in children < 15 years:
For this purpose the cumulative burden from all three strategies was considered (Fig. 4.) Data obtained through the cross sectional approach in the study is indicative of the existing pool of HIV infection among children in the district for the point in time. Assuming other methods of transmission is nil, the vertical transmission of HIV (strategy I) adds to the existing pool. Mortality among the infected children decreases the existing pool. The total number of children in the existing pool of HIV infection in Belgaum district in the study is the sum of children HIV positive in Strategy I and II, and newly identified children from Strategy III, this is given in Table 7.

Figure 4. Conceptualization of calculating the burden of HIV among Children

Table 7
Calculation of existing pool of Paediatric (< 15 years) HIV infection

Strategy	HIV Prevalence (%)	HIV pool of infection
1 & 2	10.5	3199
3	2.2*	67
Total	-	3266
* additional HIV detected from sick children, not previously identified in families.		

Figure 4. Conceptualization of calculating the burden of HIV among Children

Thus, the existing pool of HIV infection in the district works out to be 3266 HIV positive children < 15 years of age, among a mid-year (2013) projected child population of 1401688, thus giving us an overall HIV prevalence among children of 0.23%. The proportion of children among all people living with HIV in the district works out to 10.4% (3266/ (3266 + 28119)

Assuming that other methods of transmission of HIV to children < 15 years of age group is nil, the net annualized cumulative incidence rate (%) of vertical transmission of HIV per 100 pregnancies is 5.2% by about 22 months of child's age.

Discussion

This is the first district wide study estimating the Paediatric HIV burden in India. The findings indicate that Belgaum district had an overall HIV prevalence of 0.23% among children (0–14 years) and about 3266 children living with HIV, during the year 2013, making the proportion of Pediatric infections 10.4% of all HIV infections in the district. This is about a third higher than the national estimates (based on projections of adult infections) ranging between 6–7% of all HIV infections, during the same period[17, 18]. The results of

this study could be generalized to other similar districts with high HIV prevalence, high coverage of HIV screening during pregnancy/delivery and high levels of treatment coverage among those living with HIV[19]. The results although not generalizable across all districts in India, do provide useful information on how to estimate the burden of Paediatric HIV from existing data by using an excel based software (being published elsewhere).

The GBD framework[1] based on Spectrum and EPP use multiple methodological improvements, yet face limitations and biases due to use of variable data sources. A non-parametric back calculation method[20] used in Thailand studied HIV/AIDS trends for future predictions reported data adjustments to overcome surveillance reporting issues. Moreover, these methods did not include pediatric age groups. Present study is a sincere effort and a step further in deriving the pediatric burden estimate from real time data of a district.

The uniqueness of this study is its innovative epidemiological design, using robust combination of community and facility level data, inclusion of private and public sector health facility data, multi-pronged strategy of using cross-sectional and longitudinal data collection techniques, and extrapolation to correct for gaps in coverage using inflation factors. In most countries, including India, linkage loss tends to occur at various levels within the PMTCT programs[21, 22, 23, 24]. The study staff supported the program to reduce the gaps in HIV testing and treatment linkages at various levels. They thus achieved high levels of coverage of testing of children identified within the families of index person living with HIV, as well as timely testing of the HIV exposed newly delivered infants. With well-defined line listing and recruitment processes in place and individualized follow ups the study was able to quantify and reduce duplication and to better understand mobility of PLHIV within and outside the district. A number of doctors were also trained in the use of the Modified Integrated Algorithm based on IMCI-HIV and adapted IMAI guidelines, during the study. The response rates of eligible subjects for HIV testing were high with about 85% of eligible mothers completing the protocol for follow up and a similar proportion of eligible families with children completing HIV testing for all children. The study methodology is replicable for other settings and other diseases.

However, we also recognize a number of limitations in the study. During the study period, a number of changes in policy of HIV treatment and prophylaxis for pregnant women occurred including prophylaxis using single dose Nevirapine, to use of expanded regimens to option B, option B + and a ‘treat all HIV infected pregnant women’, irrespective of CD4 count, at the time of HIV diagnosis. HIV related prevention and treatment services were already district-wide and to scale. As a result of prevention and treatment initiatives, there were steady declines in HIV prevalence among the general population, and particularly among pregnant women that led to a delay in completion of the required sample size and follow up in strategy I. This delayed the timely achievement of required sample size and could have implications in our calculation of prevalence using the base population size for the district. However, because of the large overall population size within Belgaum district, the effect of these annual changes in estimated population size may not be substantial.

A second limitation is the assumption of a similar prevalence among the non-included subjects within the study, during the extrapolation exercise. The number of variables that we had collected was insufficient to

completely match the characteristics of responders with non-responders. The non-response bias could make our estimate an under or an overestimate. However, with high levels of coverage as in the study, this too may not be much different.

There was a delay in initiation of strategy III, as development of the Modified Integrated Algorithm by the national experts/ICMR sub-committee took time, as did the training of health care providers in selected talukas. 86 of the 97 HIV positive children knew their HIV positive status before falling sick. This could be attributed to the late initiation. However, despite this, strategy III did yield new HIV positives among children attending a health facility for reasons other than HIV treatment.

Our study only considered children within a family unit. We did not include children who lived without a parent (child-headed homes) or who lived within an institution. Previous studies and strategy 3 results indicate that children who were orphans were much more likely to be HIV infected. We did pick up some of the HIV infected orphans in strategy 3. However, we were not able to estimate the HIV prevalence among orphans. A cross-sectional survey of orphanages for HIV prevalence could have added value to this study[25].

Another primary assumption used in strategy I was that the new cases were contributed only by mother to child transmission. Recent studies from other countries have indicated that adolescents orphaned as a result of HIV are at greater risk and vulnerability for physical and sexual abuse, including HIV[26]. However, it is expected that these other modes of HIV transmission are rare and the numbers that add to the burden would be minimal. A last limitation is that we could not integrate mortality and migration estimates into this estimation. The study was not designed to systematically measure mortality among children living with HIV and the information on age-specific mortality rates for children 0–14 years are not available. We could not calculate age-specific death dates from the current study, as reporting of data for child deaths in the family were not forthcoming and the records were not available to verify the actual date of death, even when they were reported. We observed that HIV prevalence among the under 5 year age group was more than twice the HIV prevalence in the children 5–14 years. Interventions for PMTCT in Belgaum were almost non-existent ten years prior to the study period. Therefore, the only plausible reason for this reduction in prevalence in a cross-sectional strategy II could be that most children living with HIV had died. The non-integration of mortality information into the estimate, could result in a higher than the real value.

Despite these limitations, the study is the first of its kind in India and offers new information on methods to estimate Paediatric HIV. We put forward a number of recommendations for further studies. During the phase II ongoing study, it would also be useful to explore the feasibility of testing the baby for HIV at birth[27], as many maternally exposed new-born died before they were due for the first HIV test at six weeks. Testing for HIV at birth is a current recommended CDC guideline that has not yet been adopted in India[28]. Prolonged breast-feeding beyond six months, directly increases the risk of HIV infection, especially when it is not exclusive[2]. The acquisition of HIV infection among the children of age group post 22 months need to be further explored by ensuring follow up HIV testing of the child at least 4–6 weeks following cessation of breast feeding. A cohort study of all children within sampled family units impacted by HIV would also provide insights into mortality and morbidity among non-infected and HIV infected children, into their nutritional health status and the influence of the health status of the mothers living with HIV[30]. It is

acknowledged that there could be other reasons for HIV transmission to children, especially amongst adolescents[31]. A cohort study among adolescents within these families could indicate the extent to which this occurs.

Conclusion

The study has used a unique innovative methodology for disease burden estimation of pediatric HIV in a high prevalence district in India, where such data do not exist. There is an increase in the burden estimate from the earlier projected figure of 6–10.4% in the study; it could be used by program planners for improvement in disease control efforts. The study methodology can be replicated in similar settings for HIV as well as for other infectious diseases.

Abbreviations

HIV: human immunodeficiency virus; AIDS: Acquired immune deficiency syndrome; NACP: National AIDS Control Program; WHO: The World Health Organization, UNAIDS: The united nations' Programme on HIV and AIDS; EMTCT: Elimination of Mother-to-Child transmission of HIV and syphilis; ICTC: integrated counselling and testing centres; MTCT mother-to-child transmission; PPTCT; prevention of parent-to-child transmission; PMTCT: Prevention of mother to child transmission; ART: Anti-retroviral therapy; DNA-PCR: Deoxyribonucleic acid -polymerase chain reaction; IMCI-HIV: Intergrated Management of Childhood Illness-human immunodeficiency virus; IMAI: Integrated Management of Adolescent and Adult Illness (IMAI); KSAPS: Karnataka State AIDS Prevention Society; DAPCU: District AIDS Prevention and Control Unit; PAG: Project Advisory Group; SAP: Statistical Analytical Plan; PLHIV: Persons living with HIV; FSW: Female sex worker; MSM: Men who have sex with men; IDU Injecting drug users; EPP: Estimation and Projection Package; CDC: Centers for Disease Control; CD4: Cluster of differentiation 4.

Declarations

Ethics approval and consent to participate: Regulatory approvals for the study were obtained from the National AIDS Control Organisation (NACO) and the Karnataka State AIDS Prevention Society (KSAPS). Ethical approval was obtained from the Institutional Ethics Committee of St John's Medical College and Research Institute, Bengaluru, India. Informed written consent was taken from all the study participants. Informed written consent was taken from the entire parent on behalf of the children under the age of 16 for participating in the study. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication: Not applicable

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available. The study data is available only to the collaborating scientists. The data may be available on request to the corresponding author Dr. Anju Sinha (apradhandr@gmail.com), Indian Council of Medical Research (ICMR), New Delhi. The data also may be available upon request for some of the

collaborating institutions. Data will be sanitised to remove individual identifiers in order to comply with the local data protection laws. All data sharing is also subject to National AIDS Control Organisation (NACO) and ICMR approval.

Competing interests: Authors declare that they do not have any competing interests..

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Authors' contribution: AS conceptualized the study, wrote the protocol, coordinated the study, contributed to analysis, and revised the draft manuscript. RW was responsible for study implementation, contributed to the study design, data analysis & interpretation, wrote the first draft of the manuscript. RS was responsible for the day to day management of field activities, supervised and monitored implementation, contributed to data analysis, RSP helped with data management and analysis, SI contributed to sample size calculation and reviewed the data analysis, RMP guided the statistical plan of analysis, contributed to data analysis and interpretation. VT was involved in initial phase of study conceptualization and supervision. All authors agreed and approved the final draft for submission.

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References

1. Frank TD, Carter A, Jahagirdar D, Biehl MH, Douwes-Schultz D, Larson SL, et al. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2017, and forecasts to 2030, for 195 countries and territories: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. Lancet HIV. 2019;6(12):e831–59. doi: 10.1016/S2352-3018(19)30196-1. Epub 2019 Aug 19. PubMed PMID: 31439534; PubMed Central PMCID: PMC6934077.
2. Luzuriaga K, Mofenson LM. Challenges in the elimination of pediatric HIV-1 infection. N Engl J Med. 2016;374(8):761–70.
3. Mahy M, Penazzato M, Ciaranello A, Mofenson L, Yianoutsos CT, Davies M-A, et al. Improving estimates of children living with HIV from the Spectrum AIDS Impact Model. AIDS. 2017;31:S13–22.

4. Romain Silhol, Simon Gregson, Constance Nyamukapa et al, “Emperical Validation of the UNAIDS Spectrum model for subnational HIV estimates: case study of children and adults in Manicaland, Zimbabwe”, AIDS 2017, April: 31 (Suppl 1) S41-S50
5. Silhol R, Gregson S, Nyamukapa C, Mhangara M, Dzangare J, Gonese E, et al. Empirical validation of the UNAIDS Spectrum model for subnational HIV estimates: Case-study of children and adults in Manicaland, Zimbabwe. AIDS. 2017;31:S41–50.
6. Age structure and marital status. Office of the Registrar General & Census Commissioner, India Ministry of Home Affairs, Government of India. Available at: http://censusindia.gov.in/Census_And_You/age_structure_and_marital_status.aspx: Accessed 02 Jan 2021.
7. NACO, India. HIV Estimations: Technical Report. http://naco.gov.in/sites/default/files/HIV%20Estimations%202017%20Report_1.pdf. Accessed 02 Jan 2021.
8. Paediatric HIV Surveillance Among Infants and Children Less Than 18 Years of Age. 2013. https://www.who.int/hiv/pub/surveillance/2013package/module5/en/. Accessed 02 Jan 2021.
9. Ng’eno B, Mwangi A, Ng’ang’a L, Kim AA, Waruru A, Mukui I, et al. Burden of HIV infection among children aged 18 months to 14 years in Kenya: Results from a nationally representative population-based cross-sectional survey. J Acquir Immune Defic Syndr. 2014;66:S82–8.
10. Paving the way to end HIV - National Strategic Plan to End HIV 2017-2024. 2017. http://naco.gov.in/sites/default/files/Paving%20the%20Way%20for%20an%20AIDS%2015122017.pdf. Accessed 02 Jan 2021.
11. Penazzato M, Lule F, Essajee S. Paediatric HIV: the unfinished business. Lancet HIV. 2017;4(10):e425–7.
12. Marston M, Becquet R, Zaba B, Moulton LH, Gray G, Coovadia H, et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. Int J Epidemiol. 2011;40(2):385–96.
13. Sheahan A, Feinstein L, Dube Q, Edmonds A, Chirambo CM, Smith E, et al. Early antiretroviral therapy initiation and mortality among infants diagnosed with HIV in the first 12 weeks of life: Experiences from Kinshasa, DR Congo and Blantyre, Malawi. Pediatr Infect Dis J. 2017;36(7):654–8.
14. Arpadi SM, “Growth failure in children with HIV infection”, J Acquir Immune Defic Syndr.2000 Oct 1;25 Suppl 1:S37-42.
15. Sinha A, Nath A, Sethumadhavan R, Isac S, Washington R. Research protocol for an epidemiological study on estimating disease burden of pediatric HIV in Belgaum district, India. BMC Public Health. 2016;16(1). doi.org/10.1186/s12889-016-3132-8
16. Banandur, P., Rajaram, S.P., Mahagaonkar, S.B. et al.Heterogeneity of the HIV epidemic in the general population of Karnataka state, south India. BMC Public Health **11,** S13 (2011). https://doi.org/10.1186/1471-2458-11-S6-S13
17. Sinha A, Washington R, Sethumadhavan R, Perumal V, Potty RS, Isac S. Modified Integrated Algorithm for detection of HIV among sick children aged 0-14 year seeking care at healthcare facilities in India.

Indian Pediatr. 2020;57(7):631–5.

18. NACO/NIMS. India HIV Estimations http://naco.gov.in/sites/default/files/India%20HIV%20Estimations%202015.pdf. Accessed 02 Jan 2021.
19. Annual report, 2012-13. http://www.naco.gov.in/sites/default/files/Annual%20report%202012-13_English.pdf. Accessed 02 Jan 2021.
20. Punyacharoensin N, Viwatwongkasem C. Trends in three decades of HIV/AIDS epidemic in Thailand by nonparametric backcalculation method. AIDS. 2009; 23(9):1143
21. Mukherjee S, Ghosh S, Goswami DN, Samanta A. Performance evaluation of PPTCT (Prevention of parent to child transmission of HIV) programme: an experience from West Bengal. Indian J Med Res. 2012;136(6):1011–9.
22. Rawizza HE, Chang CA, Chaplin B, Ahmed IA, Meloni ST, Oyebode T, et al. Loss to follow-up within the prevention of mother-to-child transmission care cascade in a large ART program in Nigeria. Curr HIV Res. 2015;13(3):201–9.
23. Goga A. Birth HIV testing and paediatric treatment programmes. Lancet HIV. 2018;5(12):e675–6.
24. Prevention of mother-to-child transmission (PMTCT) of HIV. Avert.org. 2015. https://www.avert.org/professionals/hiv-programming/prevention/prevention-mother-child. Accessed 02 Jan 2021.
25. Cohn J, Whitehouse K, Tuttle J, Lueck K, Tran T. Paediatric HIV testing beyond the context of prevention of mother-to-child transmission: a systematic review and meta-analysis. Lancet HIV. 2016;3(10):e473-81.
26. Kidman R, Anglewicz P. Are adolescent orphans more likely to be HIV-positive? A pooled data analyses across 19 countries in sub-Saharan Africa. J Epidemiol Community Health. 2016;70(8):791–7.
27. Sandbulte MR, Gautney BJ, Maloba M, Wexler C, Brown M, Mabachi N, et al. Infant HIV testing at birth using point-of-care and conventional HIV DNA PCR: an implementation feasibility pilot study in Kenya. Pilot Feasibility Stud. 2019;5:18.
28. HIV/AIDS Treatment Guidelines. https://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv/55/diagnosis-of-hiv-infection-in-infants-and-children. Accessed 02 Jan 2021.
29. Potty RS, Sinha A, Sethumadhavan R, Isac S, Washington R. Incidence, prevalence and associated factors of mother-to-child transmission of HIV, among children exposed to maternal HIV, in Belgaum district, Karnataka, India. BMC Public Health. 2019;19(1):386.
30. Isanaka S, Duggan C, Fawzi WW. Patterns of postnatal growth in HIV-infected and HIV-exposed children. Nutr Rev. 2009;67(6):343–59.
31. Children, HIV and AIDS. 2015. https://www.avert.org/professionals/hiv-social-issues/key-affected-populations/children. Accessed 02 Jan 2021.

Figures

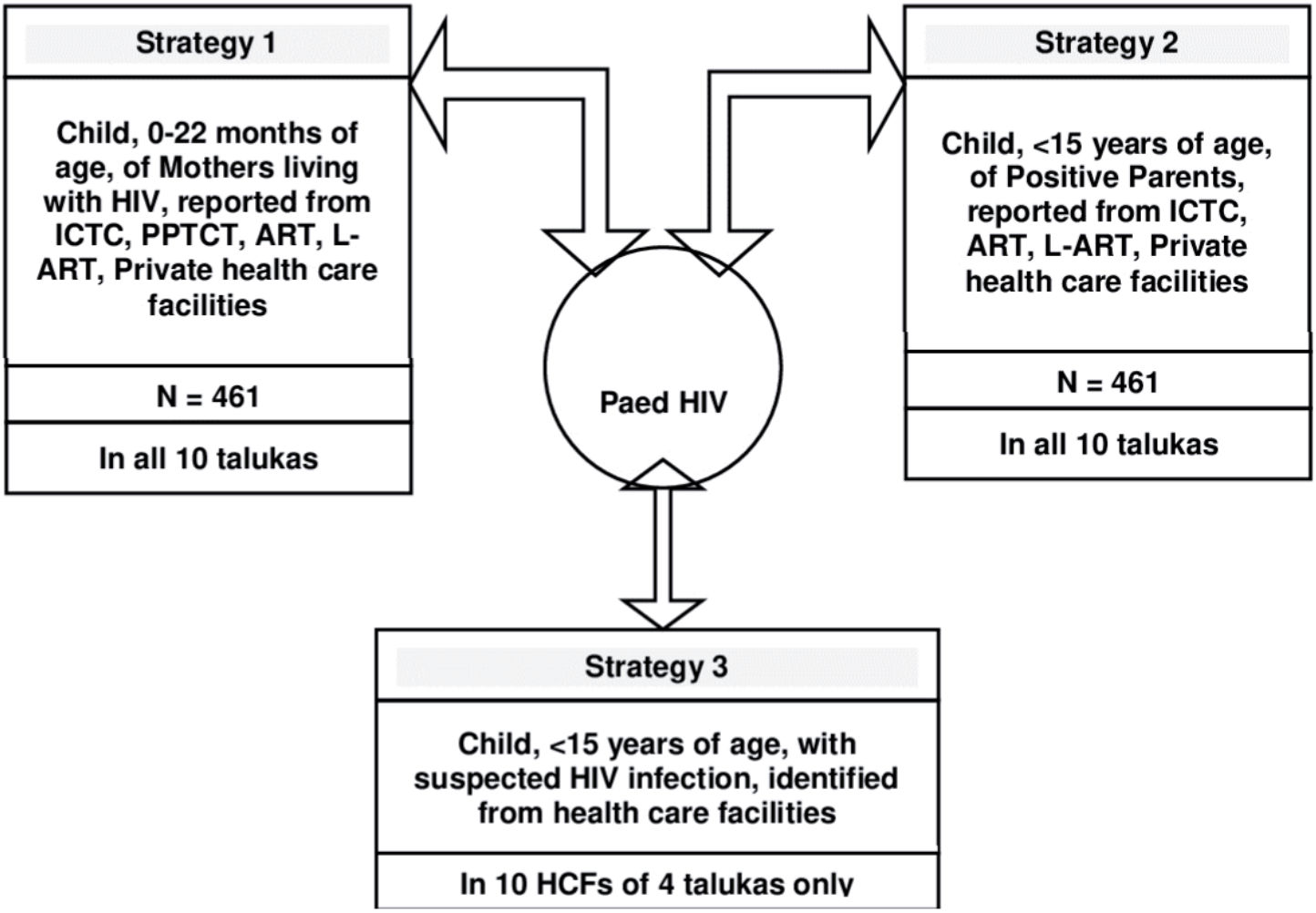

Figure 1

Outline of the research study

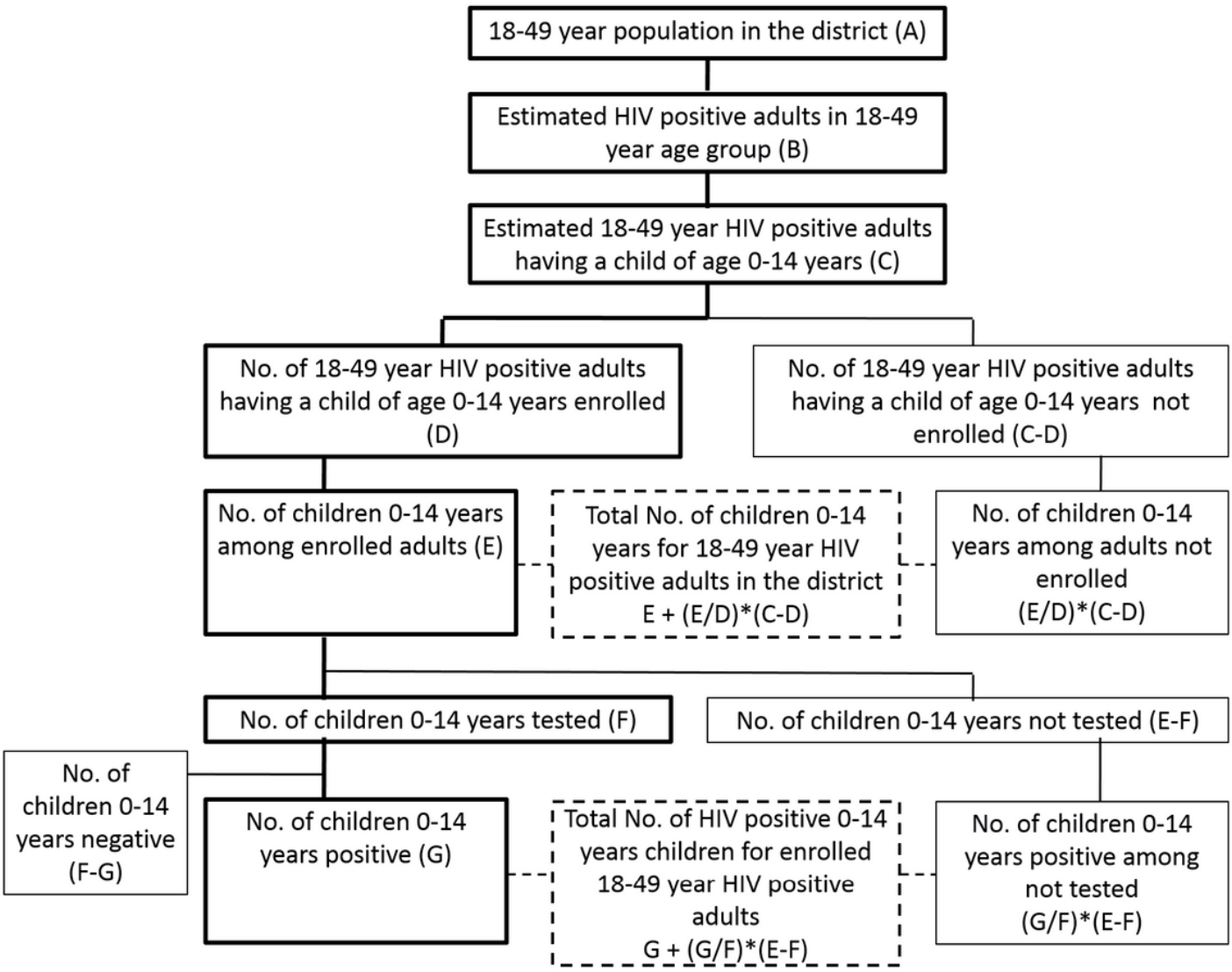

Figure 3

Conceptual diagram for calculating inflation factors and burden of Paediatric HIV from Strategy 2.