Investigations and monitoring for children and adolescents diagnosed with HIV

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Date of Preparation: June 2003, updated July 2024
Next review date: July 2026

Aim: This best practice guidance summaries the baseline and subsequent monitoring investigation for infants, children and adolescents under 18 years of age living with HIV.

History:

Birth:	Mode of delivery; duration of rupture of membranes; other infections e.g. chorioamnionitis; birth weight; infant feeding e.g. breast feeding and duration; maternal health including other STI's; and antenatal HIV test result.
Past medical history:	Previous infections (e.g. oral candida); swollen lymph nodes; chronic diarrhoea; failure to thrive and nutritional history; recurrent URTIs; childhood exanthems (e.g. chickenpox, rubella); skin infections (e.g. warts, molluscum); severe infections; hospitalisations; transfusions and IM injections; TB risk factors; immunisations; developmental history; and sexual history.
Social history:	Name and relationship of adult accompanying child; who has parental responsibility; deaths of parents or siblings; significant previous caregivers; travel history; housing; and social circumstances; school attendance and performance. HIV testing status of family members.
Drug history:	Previous antiretroviral exposure: in-utero / peripartum / as treatment in another country; other current drugs. Children newly arrived from abroad may be on combination ARV tablets not available in this country; check with a specialist HIV pharmacist. Allergies.
Examination:	Full examination including: mouth; lymph nodes; parotids; chest; liver; spleen; skin; neurology; developmental assessment, growth (ht, wt, OFC, BMI); pubertal stage, BCG scar

First line HIV diagnostic tests:
Infant < 18 months of age: HIV antibody test and HIV RNA PCR (preferred to HIV DNA PCR in local lab with faster results available).
* NB in the first weeks after delivery an infant at risk of HIV may have a negative RNA PCR.
Child > 18 months of age: HIV antibody test

Confirmatory HIV test:
HIV RNA PCR viral load and assessment of severity of HIV disease. If HIV clinically very likely or known perform both first and second line tests together.

See CHIVA HIV Testing guidelines:
https://www.chiva.org.uk/infoprofessionals/guidelines/testing/

Baseline Investigations: new diagnosis or transfer of care

HIV parameters	CD4 count and percentage with CD4:8 ratio HIV RNA PCR (VL) Baseline HIV resistance including integrase resistance (and maternal resistance if an infant) if detectable VL HIV DNA PCR if infant under 4 weeks of age HLA-B*5701
Haematology	FBC + film Sickle cell and G6PD deficiency screen (if appropriate racial group) Iron studies Consider malaria film if recently arrived from endemic area
Biochemistry	U+E, Creat Glucose TSH Vitamin D Ca, PO_4 Amylase Albumin LFT's Lipids Total protein (globulin) Urine dip (mid-stream) – if 1+ or more protein send urine protein/Cr and albumin/Cr ratio (ideally early morning sample)
Serology	Hepatitis A IgG, HBsAg, anti-HBsAb, anti-HBcAb, HCV IgG, syphilis serology, IgG for EBV, CMV, HSV, VZV, toxoplasmosis, CRAG In children over 1 year vaccine serology as per CHIVA vaccination guideline: measles, rubella, tetanus, Strongyloides if recently arrived from endemic area NB. Low CD4 count can affect serology results and PCRs should be considered
Viral PCRs	CMV PCR should be undertaken in infants & children/adolescents with advanced disease HCV PCR – should be undertaken in infants at risk of exposure and all those with advanced disease (this can be positive even if the child is HCV antibody negative) and in all with positive HCV IgG
Cultures / PCRs	According to symptoms / travel history: Stools (including ova, cysts and parasites) / urine / throat swabs / blood cultures / malaria film & antigen testing / sexual health screen if past sexual activity
TB screening	CXR, IGRA/ TB-Elispot If active TB or NTB suspected – consider gastric aspirate, induced sputum, BAL, BMA, tissue biopsy etc
Clinical Investigations	BP, urinalysis, height / weight / BMI / OFC Formal ophthalmological examination
Radiology	Baseline CXR Consider bone age (if small for age) with advice of endocrine specialist Infants / children with neurological signs, neurodevelopmental delay or evidence of congenital infections: MRI brain Abdominal US scan – if concerns about disseminated TB/NTB
Development Assessment	Full formal baseline neurodevelopment/neuropsychology assessment if available or clinically indicated

VL; viral load, BP; blood pressure, OFC; occipital frontal circumference, BMI; body mass index, CRAG; cryptococcal antigen, TB; tuberculosis, NTB; non tuberculous mycobacteria, CXR; chest xray, IGRA; interferon gamma release assay, BAL; broncho alvealor lavage, BMA; bone marrow aspirate

Pneumocystis Prophylaxis

Infants < 12 months of age	Children > 1 year of age
If > 6 weeks and under 12 months of age, start Co-trimoxazole irrespective of CD4 count	Start Co-trimoxazole 1-4 yrs: CD4 count <15% or <500 x 10^6/L 5 yrs or older: CD4 count <15% or <200 x 10^6/L

Important:

1. Any child that is diagnosed with HIV and was born in the UK, should be investigated as an incident and reported back to the obstetric unit where they were born, as all infant infection is potentially preventable.
2. The child's clinical stage should be assessed according to WHO and/or CDC criteria. More information on treatment of children and adolescents living with HIV is found in the EACS/PENTA guidelines: https://penta-id.org/hiv/treatment-guidelines/
3. Newly diagnosed children/ those transferring from abroad should be discussed with the lead regional centre and consider referral to the Perinatal Virtual Clinic https://www.chiva.org.uk/ourworkprof/regional-networks/perinatal-virtual-clinic/
4. All newly diagnosed children and those who have transferred care from abroad should be reported to the Integrated Screening Outcome Surveillance Service (ISOSS), formerly NSHPC https://www.ucl.ac.uk/integrated-screening-outcomes-surveillance/
5. All family members should receive blood born virus screening.

Monitoring Investigations for a child/adolescent on ART

- These investigations should be carried out following initiation of ART and repeated as clinically indicated, with more frequent monitoring required until viral suppression is achieved.
- In the early weeks after starting or switching ART when toxicities are most likely to arise, the biochemistry and haematology investigations and VL should be repeated within 4 weeks of starting therapy.
- HIV viral load should be repeated at every visit until sustained viral suppression is achieved
- For stable patients on suppressive ART routine assessments may occur at the following intervals:
  - age 1-3 yrs 3 monthly due to rapid growth requiring ART adjustment
  - age 4-13 yrs 4 monthly
  - age 14-18 yrs 6 monthly ideally within the school holidays in years 10-13
- Bloods for drug toxicity and CD4 parameters can be taken annually if the child/adolescent is stable on suppressive ART with no ongoing toxicity or adherence concerns.

Monitoring Investigations on ART

HIV parameters	HIV RNA PCR (viral load; VL)	1 month after starting ART, then 1-2 monthly until undetectable (VL<50). Once undetectable repeat 3 monthly (0-3 years), 4 monthly (4-14 years) and consider 6 monthly if sustained suppression from school year 10.
	CD4 count	Repeat annually once CD4 count is >350 or 25% in child under 4 years. Repeat 2 monthly in a child starting ART.

		Repeat in children with an episode of significant viral rebound.
	Resistance	At baseline and consider during episodes of viral rebound
Haematology	FBC	Annually if undetectable VL and stable/asymptomatic on ART. At each visit for those on AZT, co-trimoxazole and with unsuppressed VL
Biochemistry	U+E, Cr HbA1c Ca, PO_4 Glucose LFT's Lipids Vitamin D	ALT 6 monthly, Remainder annually if undetectable VL and asymptomatic on ART If on TDF requires U+E, Cr, Ca, PO_4 and urine prot/cr at each visit. Not required if on TAF
Clinical investigation	BP Growth: Height / Weight / BMI, OFC (< 5 years old)	6 monthly At each clinic visit (3-6 monthly dependent on age)
	Urine dip – if 1+ or more protein send urine protein/Cr and albumin/Cr ratio (ideally early morning)	Annually If on TDF requires U+E, Cr, Ca, PO_4 and urine protein/cr at each visit. Not required if on TAF
Additional health surveillance and screening	Immunisation serology Hepatitis B; if HBV negative at baseline requires vaccination and repeat serology	Annually and as clinically indicated HBsAb annually although if titre is >1000 can be increased to 2 years. Booster dose of vaccine if titre <10
	Pubertal and developmental screening	Assess through history with detailed assessment if indicated
	Sexual health screening	Annually in asymptomatic sexually active adolescents with interval screening if symptoms develop/known contact
	Cognitive assessment	In first year of diagnosis, in Year 5/6 prior to secondary school and during Year 9/10 if needing additional support for exams.

VL; viral load, ART; antiretroviral therapy, BP; blood pressure, OFC; occipital frontal circumference, BMI; body mass index, TDF; tenofovir disoproxil fumerate, TAF; Tenofovir alafenamide, AZT; zidovudine,

Investigations at virological failure

Virological failure (VF) is defined as a viral load of >200 c/ml confirmed with a repeat sample.
Viral load <50 c/ml is defined as undetectable.
Viral load 50-200 c/ml is defined as low level viraemia and may be tolerated on a high genetic barrier regimen (e.g. anchor drugs - dolutegravir, bictegravir, boosted darunavir, or for a child under 3 years boosted lopinavir).
A single viral load of 50-400 c/ml that returns to <50c/ml on repeat is defined as a blip.

HIV parameters	HIV RNA PCR VL	Repeat to confirm VF within 2-4 weeks
	CD4 count	

	Resistance	Include integrase sequence if on INSTI based ART
Haematology	FBC	VF may cause thrombocytopenia
Biochemistry	U+E, Cr, LFT's	VF may cause a rise in ALT
Clinical investigation	BP, Height, Weight	
	Urine dip	Proteinuria may occur at VF
Additional assessments	Assessment of adherence Assessment of potential drug-drug-interactions (DDIs) Consider co-trimoxazole prophylaxis Assessment of risk of onward transmission	Poor adherence is the commonest cause of VF DDIs include both prescribed, over the counter and herbal medication If CD4 count <200 or 15% Discussion re PEPSE, partner PrEP and partner notification
	Therapeutic drug monitoring (TDM)	TDM may be considered where there is persistent unexplained VF, DDIs, concerns re ART dosing eg in infancy, or malabsorption

VL; viral load, BP; blood pressure, VF; virological failure, ART; antiretroviral therapy, INSTI; integrase strand transfer inhibitor, PEPSE; post exposure prophylaxis following sexual exposure, PrEP; pre-exposure prophylaxis, TDM; therapeutic drug monitoring

Important:

1. Children/adolescents with new virological failure should be discussed urgently with the lead regional centre and consider referral to the Perinatal Virtual Clinic https://www.chiva.org.uk/ourworkprof/regional-networks/perinatal-virtual-clinic/
2. Children/adolescents with virological failure on low genetic barrier regimens re quire ART switch; see EACS/PENTA guidelines: https://penta-id.org/hiv/treatment-guidelines/