Appendices

D3 (Penta 21)

A randomised non-inferiority trial with nested PK to assess DTG/3TC fixed dose formulations for the maintenance of virological suppression in children with HIV infection aged 2-<15

Sponsor:

Collaborating academic groups:

Funder:

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APPENDIX I. MAXIMUM ALLOWABLE TOTAL BLOOD-DRAW VOLUMES FOR CHILDREN

The blood volumes taken from children for clinical and research purposes should not exceed maximum allowable limits for children.

Allowable blood draw limits for children:[1,2]

- For healthy children:
  - 3% total blood volume (TBV) in a 24-hour period
  - 10% total blood volume in a 30 day period
- For sick/unwell children:
  - 2.5% total blood volume in a 24 hour period
  - 5% total blood volume in a 30 day period

Estimated total blood volume for term infants (Wt >2kg) and children is 80 ml/kg.

Table AI-1: Maximum allowable total blood draw volumes

Wt, kg	TBV, ml	Max allowable volume in 24 hours, ml		Total volume in 30-days, ml	
		Unwell (2.5% TBV)	**Healthy (3% TBV)**	Unwell (2.5% TBV)	**Healthy (3% TBV)**
6	480	12	**14**	24	**48**
7	560	14	**17**	28	**56**
8	640	16	**19**	32	**64**
9	720	18	**22**	36	**72**
10	800	20	**24**	40	**80**
11-15	880-1200	22-30	**27-36**	44-60	**88-120**
16-20	1280-1600	32-40	**38-48**	64-80	**128-160**
21-25	1680-2000	42-50	**50-60**	64-100	**168-200**
26-30	2080-2400	52-60	**62-72**	104-120	**208-240**
31-35	2480-2800	62-70	**74-84**	124-140	**248-280**
36-40	2880-3200	72-80	**86-96**	144-160	**288-320**
41-45	3280-3600	82-90	**98-108**	164-180	**328-360**
46-50	3680-4000	92-100	**110-120**	184-200	**368-400**

*Adapted from Jack 2001[2]

APPENDIX II. WHO STAGING OF HIV INFECTION

DIAGNOSTIC CRITERIA FOR WHO STAGE 1, 2, 3 AND 4 CONDITIONS IN INFANTS AND CHILDREN UNDER 15 YEARS[3]

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Clinical Stage 1		
Asymptomatic	No HIV related symptoms reported and no clinical signs on examination.	Not applicable.
Persistent generalized lymphadenopathy	Persistent swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites (excluding inguinal) without known cause.	Clinical diagnosis
Clinical Stage 2		
Unexplained persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause.	Clinical diagnosis
Papular pruritic eruptions	Papular pruritic vesicular lesions. Also common in uninfected children: scabies and insect bites should be excluded.	Clinical diagnosis
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Clinical diagnosis
Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molloscum may indicate more advanced immunodeficiency	Clinical diagnosis
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed.) Proximal white subungual onchomycosis is uncommon without immunodeficiency	Clinical diagnosis
Recurrent oral ulcerations	Current event plus at least one previous episode in past six months. Aphthous ulceration, typically with a halo of inflammation & yellow-grey pseudomembrane.	Clinical diagnosis
Unexplained persistent parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless	Clinical diagnosis
Lineal gingival erythema	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midline	Clinical diagnosis
Recurrent upper respiratory tract infection	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB). Persistent or recurrent ear discharge.	Clinical diagnosis
Clinical Stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to −2 standard deviations from the mean (*weight-for-age for children 2-<5 years and BMI-for-age for children 5-<19years), not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management.	Documented loss of body weight of −2 standard deviations from the mean (*weight-for-age for children 2-<5 years and BMI-for-age for children 5-<19years), failure to gain weight on standard management and no other cause identified during investigation.
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment.	Confirmed by stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (>37.5C intermittent or constant for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarial agents. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Confirmed by documented fever of >37.50C with negative blood culture, negative malaria slide and normal or unchanged chest X-ray, and no other obvious foci of disease.
Oral candidiasis (after first 6-8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Confirmed by microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	Clinical diagnosis
Lymph node tuberculosis	Non acute, painless "cold" enlargement of peripheral lymph nodes, localized to one region. May have draining sinuses. Response to standard anti- tuberculosis treatment in one month.	Confirmed by histology or fine needle aspirate for Ziehl-Nielsen stain or culture.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Pulmonary tuberculosis	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. History of contact with adults with smear-positive pulmonary tuberculosis. No response to standard broad-spectrum antibiotic treatment.	Confirmed by one or more sputum positive smear for acid-fast bacilli and/or radiographic abnormalities consistent with active tuberculosis and/or culture-positive for Mycobacterium.
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	Clinical diagnosis
Symptomatic lymphocytic interstitial pneumonitis	No presumptive clinical diagnosis.	Diagnosed by chest X-ray: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may increased exercise-induced fatigue. Characteristic histology.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation	Confirmed by chest X-ray: may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), or neutropaenia (<0.5 x 109 per litre) and/or chronic thrombocytopaenia (<50 x 109 per litre)	No presumptive clinical diagnosis.	Diagnosed on laboratory testing, not explained by other non-HIV conditions, not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in WHO Integrated Management of Childhood Illness (IMCI) guidelines.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Clinical Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss stunting wasting or malnutrition not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Visible severe wasting of muscles, with or without oedema of both feet, and/or *weight-for-age for children 2-<5 years and BMI-for-age for children 5-<19 years of more than –3 standard deviations from the mean.	Documented weight-for-age *for children 2-<5 years and BMI-for-age for children 5-<19years of more than –3 standard deviations from the mean with or without oedema.
Pneumocystis pneumonia	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in WHO IMCI guidelines). Usually rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole with or without prednisolone. Chest X-ray shows typical bilateral perihilar diffuse infiltrates	Confirmed by: cytology or immunofluorescent microscopy of induced sputum or BAL or histology of lung tissue.
Recurrent severe bacterial infection, e.g. empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months	Confirmed by culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Confirmed by culture and/or histology
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs).	Difficulty in swallowing or pain on swallowing (food and fluids). In young children, suspect particularly if oral Candida observed and food refusal occurs and/or difficulties or crying when feeding.	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary or disseminated tuberculosis	Systemic illness usually with prolonged fever, night sweats, and weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis or orchiti, pericardial or abdominal	Confirmed by positive microscopy showing acid-fast bacilli or culture of Mycobacterium TB from blood or other relevant specimen except sputum or BAL. Biopsy and histology.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules.	Not required but may be confirmed by: - typical red-purple lesions seen on bronchoscopy or endoscopy; - dense masses in lymph nodes, viscera or lungs by palpation or radiology; and - histology.
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month.	Retinitis only. CMV retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Definitive diagnosis required for other sites. Histology. Cerebrospinal fluid polymerase chain reaction
CNS toxoplasmosis with onset at age over 1 month.	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Not required but confirmed by computed tomography (CT) scan (or other neuroimaging) showing single or multiple lesions with mass effect or enhancing with contrast.
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion and behavioural changes that respond to cryptococcal therapy.	Confirmed by CSF microscopy (India ink or Gram stain), serum or CSF CRAG test or culture.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: - failure to attain, or loss of, developmental milestones, loss of intellectual ability; OR - progressive impaired brain growth demonstrated by stagnation of head circumference; OR - acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.	Confirmed by neuroimaging (brain CT scan or MRI) demonstrating atrophy and basal ganglia calcification and excluding other causes.
Disseminated mycosis (coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive clinical diagnosis.	Diagnosed by: Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Disseminated mycobacteriosis, other than TB	No presumptive clinical diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung.
Chronic cryptosporidiosis	No presumptive clinical diagnosis.	Confirmed by cysts identified on modified Ziehl-Nielsen microscopic examination of unformed stool
Chronic Isospora	No presumptive clinical diagnosis.	Confirmed in children with chronic diarrhoea by microscopic examination.
Cerebral or B-cell non-Hodgkin lymphoma	No presumptive clinical diagnosis.	Diagnosed by CNS neuroimaging: at least one lesion with mass effect on brain scan; histology of relevant specimen
Progressive multi focal leukoencephalopathy	No presumptive clinical diagnosis.	Diagnosed by progressive nervous system disorder (cognitive dysfunction, gait or speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus Jacob Creutzfeldt PCR on cerebrospinal fluid
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis.	Renal biopsy
Symptomatic HIV-associated cardiomyopathy	No presumptive clinical diagnosis.	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

*Definitions for stage 3 and 4 malnutrition are modified and BMI-for-age z-scores for children 5-19 years will be used as weight-for-age z-scores reference data don't go beyond 10 years of age

WHO Child Growth Standards (z-score charts).
Weight-for-age, Girls 2-5
https://www.who.int/childgrowth/standards/cht_wfa_girls_z_2_5.pdf?ua=1
Weight-for-age, Boys 0-5
https://www.who.int/childgrowth/standards/cht_wfa_boys_z_2_5.pdf?ua=1
BMI-for-age, Girls 5-19
https://www.who.int/growthref/bmifa_girls_z_5_19_labels.pdf?ua=1
BMI-for-age, Boys 5-19
https://www.who.int/growthref/bmifa_boys_z_5_19_labels.pdf?ua=1

DIAGNOSTIC CRITERIA FOR WHO STAGE 1, 2, 3 AND 4 CONDITIONS FOR YOUNG PEOPLE 15 YEARS AND OLDER

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Clinical Stage 1		
Asymptomatic.	No HIV-related symptoms reported and no signs on examination.	Not applicable.
Persistent generalized lymphadenopathy.	Painless enlarged lymph nodes >1 cm in two or more non-contiguous sites (excluding inguinal) in the absence of known cause and persisting for three months or more.	Histology.
Clinical Stage 2		
Unexplained moderate weight loss (<10% of body weight).	Reported unexplained involuntary weight loss in pregnancy failure to gain weight.	Documented weight loss <10% of body weight.
Recurrent upper respiratory tract infections (current event plus one or more in last six-month period).	Symptom complex, such as unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media) or tonsillopharyngitis without features of viral infection (such as coryza or cough).	Laboratory studies where available, such as culture of suitable body fluid.
Herpes zoster.	Painful vesicular rash in dermatomal distribution of a nerve supply, does not cross the midline.	Clinical diagnosis.
Angular cheilitis.	Splits or cracks at the angle of the mouth not due to iron or vitamin deficiency, usually respond to antifungal treatment.	Clinical diagnosis.
Recurrent oral ulceration (two or more episodes in last six months).	Aphthous ulceration, typically painful with a halo of inflammation and a yellow grey pseudomembrane.	Clinical diagnosis.
Papular pruritic eruption.	Papular pruritic lesions, often with marked postinflammatory pigmentation.	Clinical diagnosis.
Seborrhoeic dermatitis.	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin).	Clinical diagnosis.
Fungal nail infection.	Paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discoloration – especially involving proximal part of	Fungal culture of the nail or nail plate material.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
	nail plate – with thickening and separation of the nail from the nail bed).	
Clinical Stage 3		
Unexplained severe weight loss (more than 10% of body weight).	Reported unexplained involuntary weight loss (>10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index <18.5 kg/m2; in pregnancy, the weight loss may be masked.	Documented loss of more than 10% of body weight.
Unexplained chronic diarrhoea for longer than one month.	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month.	Three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens.
Unexplained persistent fever (intermittent or constant and lasting for longer than one month).	Fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarial agents, without other obvious foci of disease reported or found on examination; malaria must be excluded in malarious areas.	Documented fever >37.5°C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection.
Persistant oral candidiasis.	Persistent or recurring creamy white curd-like plaques that can be scraped off (pseudomembranous) or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Clinical diagnosis.
Oral hairy leukoplakia.	Fine white small linear or corrugated lesions on lateral borders of the tongue that do not scrape off.	Clinical diagnosis.
Pulmonary tuberculosis (current).	Chronic symptoms: (lasting at least 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats; PLUS EITHER positive sputum smear; OR negative sputum smear; AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, caritation, pulmonary fibrosist shrinkage. No evidence of extrapulmonary disease.	Isolation of M. tuberculosis on sputum culture or histology of lung biopsy (with compatible symptoms).
Acute necrotizing ulcerative gingivitis or	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour	Clinical diagnosis.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
necrotizing ulcerative periodontitis.	and rapid loss of bone and/or soft tissue.	
Severe bacterial infection (such as pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia and severe pelvic inflammatory disease).	Fever accompanied by specific symptoms or signs that localize infection and response to appropriate antibiotic.	Isolation of bacteria from appropriate clinical specimens (usually sterile sites).
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109 per litre) or chronic (more than one month) thrombocytopaenia (<50 × 109 per litre).	Not presumptive clinical diagnosis.	Diagnosed on laboratory testing and not explained by other non-HIV conditions; not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in relevant national treatment guidelines, WHO Integrated Management of Childhood Illness guidelines or other relevant guidelines.
Clinical Stage 4		
HIV wasting syndrome	Unexplained involuntary weight loss (>10% baseline body weight), with obvious wasting or body mass index <18.5; PLUS EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month; OR reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarial agents; malaria must be excluded in malarious areas.	Documented weight loss (>10% of body weight); PLUS EITHER two or more unformed stools negative for pathogens; OR documented temperature of >37.5°C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged chest X-ray.
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever; AND Chest X-ray evidence of diffuse bilateral interstitial infiltrates; AND	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
	No evidence of bacterial pneumonia; bilateral crepitations on auscultation with or without reduced air entry.	
Recurrent bacterial pneumonia (this episode plus one or more episodes in last six months)	Current episode plus one or more previous episodes in the past six months; acute onset (<2 weeks) of severe symptoms (such as fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or chest X-ray; response to antibiotics.	Positive culture or antigen test of a compatible organism.
Chronic herpes simplex virus infection (orolabial, genital or anorectal) of more than one month or visceral infection of any duration.	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrence of herpes simplex virus infection and reported for more than one month. History of previous episodes. Visceral herpes simplex virus requires definitive diagnosis.	Positive culture or DNA (by polymerase chain reaction) of herpes simplex virus or compatible cytology or histology.
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidasis.	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy or histology.
Extrapulmonary tuberculosis	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated tuberculosis varies by site: Pleural, pericardia, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or ostetis. Discrete peripheral lymph node Mycobacterium tuberculosis infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis.	M. tuberculosis isolation or compatible histology from appropriate site or radiological evidence of miliary tuberculosis; (diffuse uniformly distributed small miliary shadows or micronodules on chest X-ray).
Kaposi sarcoma	Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or violaceous colour, skin lesions that usually develop into plaques or nodules.	Macroscopic appearance at endoscopy or bronchoscopy, or by histology.
Cytomegalovirus disease (other than liver, spleen or lymph node)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal hitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal	Compatible histology or cytomegalovirus demonstrated in cerebrospinal fluid by culture or DNA (by polymerase chain reaction).

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
	vasculitis, haemorrhage and necrosis.	
Central nervous system toxoplasmosis	Recent onset of a focal nervous system abnormality consistent with intracranial disease or reduced level of consciousness AND response within 10 days to specific therapy.	Positive serum toxoplasma antibody AND (if available) single or multiple intracranial mass lesion on neuroimaging (computed tomography or magnetic resonance imaging).
HIV encephalopathy	Disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection that might explain the findings.	Diagnosis of exclusion: and (if available) neuroimaging (computed tomography or magnetic resonance imaging).
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy.	Isolation of Cryptococcus neoformans from extrapulmonary site or positive cryptococcal antigen test on cerebrospinal fluid or blood.
Disseminated nontuberculous mycobacteria infection	No presumptive clinical diagnosis.	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding the lungs.
Progressive multifocal leukoencephalopathy	No presumptive clinical diagnosis.	Progressive nervous system disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive polyomavirus JC polymerase chain reaction on cerebrospinal fluid.
Chronic cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive clinical diagnosis.	Cysts identified on modified Ziehl-Nielsen stain microscopic examination of unformed stool.
Chronic isosporiasis	No presumptive clinical diagnosis.	Identification of Isospora.
Disseminated mycosis (coccidiomycosis or histoplasmosis)	No presumptive clinical diagnosis.	Histology, antigen detection or culture from clinical specimen or blood culture.
Recurrent non-typhoid Salmonella bacteraemia	No presumptive clinical diagnosis.	Blood culture.
Lymphoma (cerebral or B-cell non-Hodgkin)	No presumptive clinical diagnosis.	Histology of relevant specimen or, for central nervous system

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
		tumours, neuroimaging techniques.
Invasive cervical carcinoma	No presumptive clinical diagnosis.	Histology or cytology.
Atypical disseminated leishmaniasis	No presumptive clinical diagnosis.	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen.
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis.	Renal biopsy.
Symptomatic HIV-associated cardiomyopathy	No presumptive clinical diagnosis.	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography.

APPENDIX III. PRODUCT INFORMATION – UNREGISTERED PRODUCTS

The following unregistered products will be supplied for the trial by ViiV Healthcare Ltd:

DTG 5 mg paediatric dispersible tablets are white, round, film-coated, and debossed with 'SV H7S' on one side and '5' on the opposite side. Each tablet contains 5.26 mg dolutegravir sodium, which is equivalent to 5 mg of dolutegravir free acid. The tablets are designed to be dispersed in small amount of water prior to oral administration. The tablets are packaged in HDPE bottles with child-resistant closures that include an induction seal and a desiccant. Store and dispense in the original package, protect from moisture, and keep bottles tightly closed. Do not remove desiccant. The tablets should be stored up to 30°C (86°F).

Dolutegravir/Lamivudine Dispersible Tablets, 5mg/30mg are white, film-coated, oval, biconvex tablets for oral administration. The tablets are debossed with 'SV53' on one side and plain on the other side. The tablets contain 5.26mg dolutegravir sodium (equivalent to 5mg dolutegravir) and 30mg lamivudine. The tablets are designed to be dispersed in a small amount of water prior to administration. The tablets are packed into HDPE bottles with desiccant and child-resistant closures that include an induction seal. The bottles may contain a desiccant. Protect from moisture, and keep bottles tightly closed. The tablets should be stored up to 30°C (86°F).

Dolutegravir/Lamivudine Tablets, 50mg/300mg are white, biconvex, oval, film-coated tablets for oral administration. The tablets are debossed with 'SV137' on one side and plain on the other side. The tablets contain 52.6mg dolutegravir sodium which is equivalent to 50mg dolutegravir free acid and 300mg lamivudine. The tablets are packaged into HDPE bottles with child-resistant closures that include an induction seal. The bottles may contain a desiccant. Protect from moisture, and keep bottles tightly closed. The tablets should be stored up to 30°C (86°F).

APPENDIX IV. TOXICITY GRADINGS AND MANAGEMENT

Adapted Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events (Corrected Version 2.1 - July 2017) [4]

Modifications to reporting:

- Neutrophil grading is based on WHO guidelines[5] recognising the lower normal levels in African populations.

	Grade 1	Grade 2	Grade 3	Grade 4
Absolute Neutrophil Count	750-<1000mm^3 0.75 x10^9 - <1x 10^9/L	500-749/mm^3 0.5 x10^9 – 0.749 x 10^9/L	250-499/mm^3 0.25 x 10^9 – 0.499 x 10^9/L	<250mm^3 <0.250 x 10^9/L

- For creatinine grading DAIDS criteria based on upper limit of normal values rather than comparison with the baseline will be used
- For creatinine clearance DAIDS ranges of estimated creatinine clearance rather than comparison with the baseline will be used

General Instructions:

If the need arises to grade a clinical adverse event (AE) that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located at the top of the table.

If the severity of an AE could fall under either one of two grades (e.g. the severity of an AE could be either Grade 2 or Grade 3) select the higher of the two grades for the AE.

Definitions:

Basic self-care functions	Adults: Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young children: Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
Chemical pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
Hospitalisation	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labour and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
LLN	Lower limit of normal
Medical intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE
NA	Not applicable
Operative intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual social & functional activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young children: Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
CLINICAL CONDITIONS: ESTIMATING SEVERITY GRADE FOR PARAMETERS NOT IDENTIFIED IN THE GRADING TABLE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities [1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
DERMATOLOGICAL				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE and METABOLIC				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non- ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
MUSCULOSCELETAL				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
NEUROLOGICAL				
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part- time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full- time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre- existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
PREGNANCY, PEURPERIUM and PERINATAL				
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC and SLEEP PROBLEMS				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted
RESPIRATORY				
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
SENSORY				
Hearing Loss ≥ 12 years of age	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan- uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
SYSTEMIC				
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for- height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for- length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
URINARY				
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
SITE REACTIONS TO INJECTIONS AND INFUSIONS				
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness [12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life- threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life- threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
LABORATORY				
CHEMISTRY				
Acidosis	NA	pH ≥7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life- threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65* to < *2.88*	11.5 to < 12.5 *2.88* to < *3.13*	12.5 to < 13.5 *3.13* to < *3.38*	≥ 13.5 ≥ *3.38*
< 7 days of age	11.5 to < 12.4 *2.88* to < *3.10*	12.4 to < 12.9 *3.10* to < *3.23*	12.9 to < 13.5 *3.23* to < *3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63* to < *1.88*	6.0 to < 6.5 *1.50* to < *1.63*	5.50 to < 6.0 *1.38* to < *1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance [14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life- threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Phosphate, Low (mg/dL; *mmol/L*) *> 14 years of age*	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≥120 *≥120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*
HAEMATOLOGY				
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm3; x109cells/L) > 5 years of age (not HIV infected)	600 to < 650 0.600 to < 0.650	500 to < 600 0.500 to < 0.600	350 to < 500 0.350 to < 0.500	< 350 < 0.350
Absolute Neutrophil Count (ANC), Low (cells/mm^3; cells/L) > 7 days of age	800 to 1,000 0.800 x 10^9 to 1.000 x 10^9	600 to 799 0.600 x 10^9 to 0.799 x 10^9	400 to 599 0.400 x 10^9 to 0.599 x 10^9	< 400 < 0.400 x 10^9
2 to 7 days of age	1,250 to 1,500 1.250 x 10^9 to 1.500 x 10^9	1,000 to 1,249 1.000 x 10^9 to 1.249 x 10^9	750 to 999 0.750 x 10^9 to 0.999 x 10^9	< 750 < 0.750 x 10^9
≤ 1 day of age	4,000 to 5,000 4.000 x 10^9 to 5.000 x 10^9	3,000 to 3,999 3.000 x 10^9 to 3.999 x 10^9	1,500 to 2,999 1.500 x 10^9 to 2.999 x 10^9	< 1,500 < 1.500 x 10^9

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fibrinogen, Decreased (mg/dL; g/L)	100 to < 200 1.00 to < 2.00 OR 0.75 to < 1.00 x LLN	75 to < 100 0.75 to < 1.00 OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 0.50 to < 0.75 OR 0.25 to < 0.50 x LLN	< 50 < 0.50 OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; mmol/L)[17] ≥ 13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 < 4.34
≥ 13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03
57 days of age to < 13 years of age *(male and female)*	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; cells/L)	100,000 to < 125,000 100.000 x 10^9 to < 125.000 x 10^9	50,000 to < 100,000 50.000 x 10^9 to < 100.000 x 10^9	25,000 to < 50,000 25.000 x 10^9 to < 50.000 x 10^9	< 25,000 < 25.000 x 10^9
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; cells/L) > 7 days of age	2,000 to 2,499 2.000 x 10^9 to 2.499 x 10^9	1,500 to 1,999 1.500 x 10^9 to 1.999 x 10^9	1,000 to 1,499 1.000 x 10^9 to 1.499 x 10^9	< 1,000 < 1.000 x 10^9

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 7 days of age	5,500 to 6,999 5.500 x 10^9 to 6.999 x 10^9	4,000 to 5,499 4.000 x 10^9 to 5.499 x 10^9	2,500 to 3,999 2.500 x 10^9 to 3.999 x 10^9	< 2,500 < 2.500 x 10^9
URINALYSIS				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

ULN = upper limit of normal; LLN = lower limit of normal

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

[2] As per Bazett's formula.

[3] For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

APPENDIX V. LIVER SAFETY – STUDY TREATMENT RESTART OR RE-CHALLENGE GUIDELINES AND CHECKLIST

If a causal relationship between the liver event and DTG or other suspected antiretroviral drugs cannot be ruled out, then the suspected antiretroviral drug(s) must be permanently discontinued and the participant not re-challenged.

DRUG RESTART FOLLOWING TRANSIENT RESOLVING LIVER EVENTS NOT RELATED TO STUDY DRUG

Restart can be considered when liver chemistries improve to within 1.5x baseline and ALT<3xULN where:

- Liver chemistries have a clear underlying cause other than drug-induced liver injury (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury.
- If restart of TRIUMEQ or any other ABC-containing product is being considered then the participant must be HLA-B*5701 negative (even in countries where HLA-B*5701 screening is not considered standard of care).
- The participant is receiving compelling benefit and benefit of drug restart exceeds risk
- Approval from the MRC CTU at UCL and the site PI for the drug restart has been obtained.
- The participant has been provided with a clear description of the possible benefits and risks of drug restart, including the possibility of recurrent, more severe liver injury or death.
- The participant has also provided signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study file.
- Following drug restart, the participant will return to the clinic once a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations (see **Protocol Section 5.8.1.A Liver Toxicity**) are met, study drug must be stopped.

LIVER SAFETY – CHECKLIST FOR DRUG RESTART APPROVAL OR REFUSAL

"Drug restart" after discontinuation of Study Drug due to Liver Stopping Criteria (as defined in **Protocol Section 5.8.1.A Liver Toxicity**), can only be approved by the MRC CTU at UCL Trial Management Team and Site Principal Investigator for **transient, defined non-drug-induced liver injury with NO evidence of:**

- immunoallergic injury/HLA association with injury
- drug-induced liver injury
- alcoholic hepatitis

Investigators MUST:

1. Hold study drug while laboratory investigations and evaluations are completed to assess diagnosis, and not restart until "Drug restart" has been approved by the Chief Investigator, Trial Physician and Site Principal Investigator.
2. Complete the table below and submit to the MRC CTU at UCL Trial Management Team. The Liver Event case report form should already have been submitted to the MRC CTU at UCL Trial Management Team, along with liver imaging and/or liver biopsy case report forms and/or SAE case report form where applicable. Where restart of TRIUMEQ or any other ABC-containing product is being considered, provide documentation verifying HLA-B*5701 status.

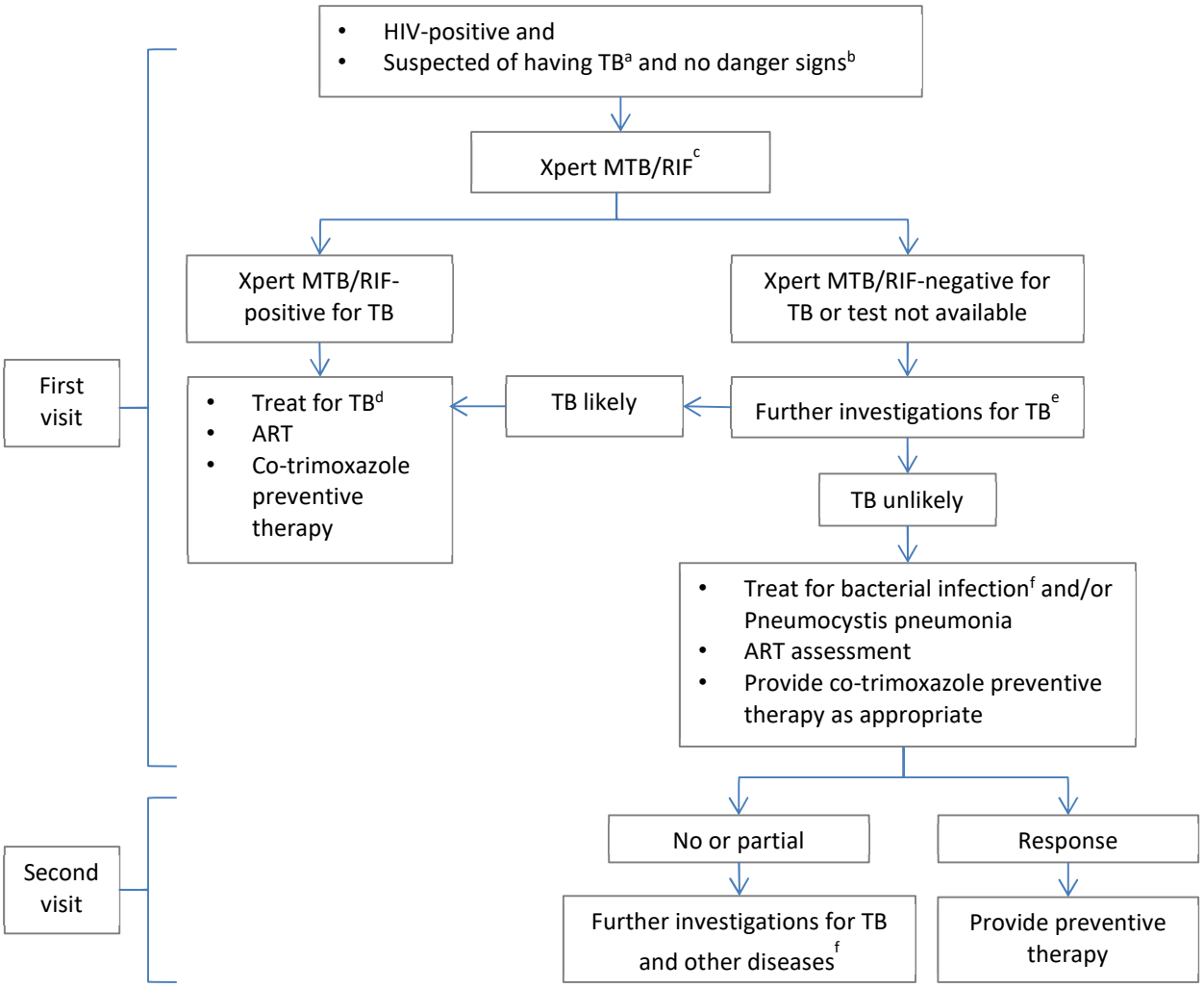
Participant Number:	**Yes**	**No**
Have liver chemistries improve to within 1.5x baseline and ALT<3xULN?		
Was participant's HIV infection stable or improving on Study Drug?		
Were any of the **following high risk factors** included in the initial liver injury event? **(Do not restart if 'Yes' for any one of the following high risk factors)**:		
• Fever, rash, eosinophilia, or hypersensitivity		
• Drug-induced liver injury		
• Alcoholic hepatitis (aspartate aminotransferase>ALT, typically <10xULN)		
• Study Drug (other than ABC) has an HLA genetic marker associated with liver injury		
For restart of TRIUMEQ, or any other abacavir-containing Study Drug, the participant MUST be HLA-B*5701 negative[1] Specify HLA-B*5701 status[2]:		

[1] In countries/regions where HLA-B*5701 pre-therapy screening is not considered standard of care, participants stopping abacavir- containing study drug due to Liver Stopping Criteria MUST be tested and found to be negative for the HLA-B*5701 allele before abacavir-containing Study Drug can be re-started.

[2] If study drug does not containing ABC then record HLA-B*5701 status as "not applicable"

APPENDIX VI. MANAGEMENT OF PARTICIPANTS WITH SUSPECTED TB

Algorithm for managing participants with suspected TB (adapted from WHO 2016 guidelines[6])



[a] Suspicion of TB is defined by the presence of any one of the following symptoms
– For adults and adolescents living with HIV: current cough, fever, weight loss or night sweats
– For children with HIV: poor weight gain, fever, current cough or history of contact with a TB case

[b] Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided

[c] For participants suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood)

[d] If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-reistant TB should be initiated. A second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and send a sample for culture and additional drug sensitivity testing

[e] Further investigations for TB include chest X-ray, clinical assessment and a repeat Xpert MTB/RIF using a fresh specimen. Send a sample for TB culture where feasible. If Xpert MTB/RIF is not available, conduct acid-fast bacillus (AFB) microscopy. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed. These investigations may require additional visits.

[f] Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used

As rifampicin interacts with many antiretroviral drugs, a change of regimen may be needed for children who develop TB in the trial. Management of children on DTG-based ART who are treated for TB is outlined in the protocol (**Protocol Section 5.9 TB Management Strategies**).

Guidance on the choice of ART for children with TB who are no longer on DTG-based ART can be found in the WHO 2021 guidelines[7] or national guidelines and may differ between countries. As efavirenz does not interact in a clinically significant manner with rifampicin, children receiving efavirenz-based ART can continue the same regimen. Children receiving lopinavir/ritonavir (LPV/r)-based ART can continue on their regimen if they receive super-boosted ritonavir (increasing ritonavir to achieve a LPV/r ratio of 1:1),[8,9] . Children on raltegravir-based ART should have their raltegravir dose doubled.[10,11] Please note, that raltegravir formulations are not interchangeable (granules and chewable tablets have ~1.3 times better bioavailability than film-coated tablets). Nevirapine, atazanavir or darunavir cannot be co-administered with rifampicin and children on these drugs should be switched to alternative antiretrovirals.

APPENDIX VII. HIGHLY-EFFECTIVE CONTRACEPTION

All female participants who are sexually active and randomised to receive DTG must use highly effective contraception.[12]

TYPE OF CONTRACEPTION	Boosted protease inhibitors (PIs)			NNRTIs				CCR5	NRTIs	Integrase		
	Atazanavir/r	Darunavir/r	Lopinavir/r	Efavirenz	Nevirapine	Etravirine	Rilpivirine	Maraviroc	All	Raltegravir	Dolutegravir	Elvitegravir/c
Combined												
Combined PILL	**Not recommended** as ↓oestrogen *but if no other acceptable option consider* ***pill (e.g. Cilest) with at least 35mcg ethinylestradiol***	**Not recommended** as ↓oestrogen *but if no other acceptable option consider* ***double dose pill and monitor symptoms***		**NOT ADVISED**	**Not recommended as** ↓ in oestrogen and progestogen exposure, unlikely to be clinically significant *but if no other acceptable option consider* ***and monitor symptoms***	**SAFE** to use with standard pill (e.g. Maexeni) ethinyestrodiol 30mcg desogestrel 150mcg	**SAFE** with all listed contraception	**SAFE** with all listed contraception	**SAFE** with all listed contraception	**SAFE** with all listed contraception	**SAFE** with all listed contraception	↓oestrogen ***use pill (e.g. Cilest) with at least 35mcg ethinylestradiol***
Progesterone only												
Progesterone only PILL (containing 75 micrograms desogestrel)	**Not recommended** as ↑ progesterone, unlikely to be significant but can consider *but if no other acceptable option consider* ***and monitor symptoms***			**NOT ADVISED**	**Not recommended as** ↓ progesterone, unlikely to be significant *but if no other acceptable option consider* ***and monitor symptoms***	**SAFE** to use, ↓ progesterone, unlikely to be significant						↑progesterone unlikely to be significant but ***monitor symptoms***
IMPLANT	**Not recommended** as ↑ progesterone, unlikely to be significant *but if no other acceptable option consider* ***and monitor symptoms***			**Not recommended** as ↓progesterone levels *but if no other acceptable option consider* ***replacing in 12 months***								
DEPO-PROVERA	**SAFE** with all ART											
MIRENA IUS	**SAFE** with all ART											
Non-hormonal												
Copper IUD	**SAFE** with all ART											
KEY	Safe to administer (note dose adjustments)			Refer to complex contraception clinic for advice, monitoring and follow up and use with caution								Not advised

Adapted, with permission, from: Hamzah L and Samuel I, June 2018

APPENDIX VIII. MODIFIED FDA SNAPSHOT ALGORITHM

Categorisation of Virological Outcomes at 48/96 weeks (within window 42-54/90-102 weeks)

A modified version of the FDA snapshot algorithm will be used to describe virological failure at weeks 48 and 96 as described in the table below (Table AVIII-1).

Table AVIII-1. Modified FDA snapshot algorithm

	DTG/3TC	SOC
	N (%)	N (%)
HIV RNA≥50 c/mL[1]		
Treatment difference (95% CI)		
HIV RNA<50 c/mL[2]		
No virological data in week 48/96 window		
Discontinued study regimen due to AE or death and last on treatment HIV-1 RNA <50 c/mL[3]		
Discontinued study regimen for other reasons and last on treatment HIV-1 RNA <50 c/mL[4]		
On study regimen[5] but missing HIV RNA data in window		

[1]Includes (i) participants on study drug (DTG/3TC) or SOC (including with prior permitted changes while HIV-RNA<50 c/mL) who had confirmed HIV-RNA≥50 c/mL in 48/96 week window; (ii) participants who changed any component of initial regimen because of lack of efficacy prior to/during week 48/96 window; (iii) participants who discontinued/changed any component of initial regimen for reasons other than lack of efficacy prior to/during week 48/96 with the last on treatment (prior to/on the date of change) HIV-1 RNA ≥50 c/mL

[2] Includes (i) participants on study drug (DTG/3TC) or SOC (including with prior permitted changes while HIV-RNA<50 c/mL) and HIV-RNA<50 c/mL at week 48/96

[3]Includes participants who discontinued any component of initial regimen for toxicity/death before or during week 48/96 where last on treatment HIV-RNA<50 c/mL

[4]Includes participants who discontinued or changed any component of initial regimen for reasons other than an AE/death or lack of efficacy, e.g., withdrew consent, lost to follow-up, pregnancy (or desire to become pregnant), transferred care to a non-study site or had non-permitted change of any component of initial regimen before or during week 48/96 where last on treatment HIV-RNA<50 c/mL

[5]DTG/3TC or SOC (including with prior permitted changes while HIV-RNA<50 c/mL)

Permitted changes to ART are specified in the protocol (**Protocol Section 5.5.1 Permitted ART Changes**). All other changes to ART are non-permitted (including stopping ART).

REFERENCES

1. Howie S. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 2011(89):46-53.
2. Jack R. Maximum allowable total blood draw volumes. Children's Hospital and Regional Medical Center Laboratory, Seattle, WA 2001 August 2001; Available from: https://www.ucdmc.ucdavis.edu/clinicaltrials/StudyTools/Documents/Blood_Draws_Maximum_Allowable.doc.
3. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. 2007. Available: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf
4. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available: https://rsc.tech-res.com/docs/default-source/safety/daidsgradingcorrecetedv21.pdf.
5. World Health Organization. Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach - 2010 revision. July 13, 2010.
6. World Health Organization. Algorithm for managing people living with HIV who are suspected of having TB (Annex 14) in 'Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection - recommendations for a public health approach (second edition)'. June 2016. Available: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1.
7. World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. July 2021. Available: https://www.who.int/publications/i/item/9789240031593.
8. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach - Second edition. June 2016. Available: http://www.who.int/hiv/pub/arv/arv-2016/en/.
9. Rabie H, Denti P, Lee J, et al. Lopinavir-ritonavir super-boosting in young HIV-infected children on rifampicin-based tuberculosis therapy compared with lopinavir-ritonavir without rifampicin: a pharmacokinetic modelling and clinical study. Lancet HIV 2018.
10. Meyers T, Krogstad P, Samson P, et al. P1101: phase I/II study of raltegravir containing regimen in HIV-TB cotreated children. Abstract 845. Conference on Retroviruses and Opportunistic Infections; March 4-7, 2018; Boston, Massachusetts (https://www.croiconference.org/sessions/p1101-phaseiii-study-raltegravir-containing-regimen-hiv-tb-cotreated-children).
11. Krogstad P, Samson P, Meyers T, et al. Phase I/II study of raltegravir-containing regimen in HIV and TB co-treated children aged 6 to <12 years. Abstract 21. 10th International Workshop on HIV Pediatrics; July 21-22, 2018; Amsterdam, Netherlands. (http://regist2.virology-education.com/abstractbook/2018/abstractbook_10ped.pdf).
12. Heads of Medicines Agencies, Clinical Trial Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. September 2014. Available: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf