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St George's University Hospitals
NHS Foundation Trust

NHS

INFECTION CARE GROUP HANDBOOK & TREATMENT GUIDELINES

Edition: August 2017

CONTENTS

1. INTRODUCTION

- This guide is intended to provide CIU clinical staff with a reference source of local information and treatment guidelines for the most frequently seen conditions.

- This guide includes a section on patient admission, CIU organization, useful telephone numbers and handling of samples.

- These guidelines represent current practice within CIU at St. George's. Only the most frequently used treatment options are described and these should be adapted according to the needs of each individual patient.

- Some regimens are as yet unlicensed, although widely-used.

- Regimens are intended for use in the treatment of adults only, unless stated.

- The advice provided about monitoring refers only to drug treatment and not the disease. It is not exhaustive, but intended to avert the commonest potential toxicities only.

- Although every effort has been made to ensure that the information provided is correct, the authors cannot be held responsible for any omissions or errors. Check the dosage with a second source of information, wherever possible. Responsibility cannot be taken for any untoward incidents that occur in patients managed according to this document. Any ideas or suggestions for improvements should be made to Prof Derek Macallan, (ext 0283, macallan@sgul.ac.uk).

What's new in this Edition – August 2017

Several sections have been updated and new links to new external guidelines added. The ARV section has been updated with the new TAF-based combination tablets. We have updated the malaria guidelines in line with new recommendations. We now also have a section on Neurocycsticercosis, thanks to Danni.

The on-line version should have updated hyperlinks to referenced web-pages. Please let me have updates and amendments in real time and we will try to keep this up to date on a rolling basis rather than making intermittent major revisions. Please also let me know which parts you use, and which you do not! I've retained the Biological Agents section for the moment, even though it feels less relevant than when we first put it in – I hope it remains that way.

Thanks to all contributors, especially Laura, Ghadeer and Chon.

Derek Macallan
August 2017

2. GENERAL NOTES AND GUIDANCE ON CIU

2.1. WEEKLY TIMETABLE

WEEKLY TIMETABLE

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
8.30 - McEntee Board Round 9:00 Consultant Ward Round *McEntee Ward*	8.30 - McEntee Board Round 9:00 HIV Clinic DCM +SpR *Courtyard Clinic* 11.00 - SpR Undergraduate Teaching	8.30 Neuroradiology meeting 9.00 - McEntee Board Round 9:30 General ID/TB Clinic CC/AH/AA/ SpR *Lanesborough B* Wed AM GUM SpR Training (*CC*)	8.30 - McEntee Board Round 9:00 Consultant Ward Round *McEntee Ward*	8.15 Journal Club *Jenner Wing* 9.00 - McEntee Board Round 10:00 Social MDT *McEntee Seminar Room* 11.00 - Consultant Undergraduate Teaching
1:30 MDT *Microbiology Seminar Room, 1st floor, Jenner Wing*	12.30 Clinical/Lab Teaching Micro Sem Rm		12:45 Grand Round *Monckton Lecture Theatre*	1:00 – 2:00 Clinical /Academic meeting *Seminar room, Courtyard Clinic*
2.00 HIV Clinic Hepatitis co-infection clinic monthly CC/AA/ AH / DCM + SpR *Courtyard Clinic*	2:00 OP Clinic Gen ID TB + SpR Plus Tropical (monthly SK) *St James OP*	2.30 Antifungal Round TB 4.00 ARV group *CC Sem Rm*	2:00 MDT *Path Sem Rm, Jenner wing* 4:00 – 6:00 HIV Clinic TH + SpR *Courtyard Clinic*	

Clinics

One CMT attends Tuesday pm Clinic (Lanesborough wing) unless only one CMT is on the ward. Ward discharges should be allocated to see Consultant / SpR / SHO according to clinical need in Tuesday or Wednesday clinics.

TB patients are seen Wednesday am in Clinic B (Lanesborough wing) 1st/3rd Wednesdays of month. The TB Nurses will also see patients in this clinic and they should be copied in to the clinic letters.

2.2. ON-CALL

CIU provides a 24-hour 7-day service for acute admissions with infection-related problems

The On-Call bleep for CIU is 7568

- This operates between 09:00 and 17:00.
- Out of hours via Switchboard

The Ward Registrar carries bleep 6036

There is also a list of contact numbers in McEntee Drs' Office - Ext 3156

There is always a Consultant on-call - available through switchboard (home/aircall/mobile).

Weekends
The on-call SpR will do a ward round on McEntee ward (and outliers) on Saturday and Sunday am, except when a joint-training Micro/ID SpR is also on-call for Micro, when a GUM SpR should cover the ward from 9-5 on Saturday and Sunday. SHO cover is from the St James Wing on-call SHO. The SpR will then do a telephone "Board Round" with the consultant on call.

Hospital at Night
Currently, the St James Wing SHO covers McEntee ward inpatients but the Lanesborough wing SHO is responsible for CIU admissions. The on-call SHO should discuss all admissions with the on-call SpR.

It is essential that the on-call SHO's and the CIU team liaise each morning to discuss any admissions, and any changes in the state of CIU in-patients. If there have been no admissions, and no change in the status of inpatients, it is still necessary to liaise to confirm this. It is important to ensure that we do not "lose" patients in the handover process.

2.3. REFERRALS

Selection of patients for referral from Emergency Department to CIU

When in doubt discuss with CIU registrar or consultant on call

Category A: Patients who should immediately be referred to, and accepted by, CIU

- Returning travellers
  This includes patients with fever or other symptoms attributable to infection or parasite infestation. Note that diseases may present several months after travel, e.g. benign malaria, amoebic liver abscess.

- Patients with known or suspected HIV infection
  HIV may also present as wasting without fever or as opportunist tumour such as KS

- Patients suspected of having acute meningitis who should be referred immediately

- Patients whose infection can be transmitted easily so they must be nursed in isolation. This includes patients with gastroenteritis, typhoid, open tuberculosis.

Category B: Patients should be discussed with the SpR on call:

- Patients with fever as the main clinical issue when an infectious cause is part of the differential diagnosis, e.g. encephalitis, atypical pneumonia, endocarditis.

Patients seen in A&E that need further tests (e.g. malarial parasites or review) but not admission, can be reviewed on McEntee Ward the next day - photocopy their A&E notes and give this to the McEntee SHO – this is for patients needing urgent review
Patients can be given blood forms to use in out-patient phlebotomy prior to ward review to reduce the workload of McEntee SHOs (but this does not apply to blood cultures). Please inform ward nursing staff of any ward attenders.

Follow-up
Follow up from A&E can also be requested for CIU out-patients – please photocopy their A&E notes and write a referral letter stating your areas of concern.

Discharges from A&E – write a letter for the GP and put a photocopy in the A&E notes.

Admissions
Hand-over all accepted admissions and referrals to the on-coming SHO.
Please record the name, patient location, DOB and hospital number in the McEntee diary so that the ward-list can be updated.

2.4. INVESTIGATIONS

Safety
Always collect and handle samples safely.
Wear gloves where appropriate.
Wear eye protection for all procedures where splashes may occur – remember especially for LP and for handling ABG syringes – especially injecting into analyser.
Dispose of sharps safely; never resheath needles.

Basic Tests for CIU admissions
Blood cultures
Yellow top serum save to microbiology
U+E LFT Glucose CRP
FBC
CXR
Urinalysis
Malaria film – If indicated by travel history – perform **3 times** if clinically indicated and initial sample negative

Lumbar Punctures
Don't delay antibiotics for LP if meningitis highly likely
Do consider need for CT scan before LP

Measure opening pressure with a manometer
Routinely collect samples for:

- Microbiology (x2 or 3 labelled sequentially if possible)
- Chemistry: CSF glucose (grey tube) and protein (no additive)
- Cytology if appropriate
- Save one bottle on McEntee ward in case needed later

Remember to take a blood glucose sample for interpretation of CSF glucose
In special circumstances may request CSF syphilis serology, Cryptococcal Ag (CrAg) and/or CSF ACE

Minimum microbiology samples for patients being admitted
THIS IS NOT AN EXHAUSTIVE LIST
N.B. if the patient is clinically unwell DO NOT delay giving antibiotics

Chest infection:
Blood cultures
Sputum (if possible) for MC&S; AFB if appropriate
Serum for atypical serology
Urine - pneumococcal/legionella urinary Ag
Throat/nose swabs for respiratory virology

Meningitis:
Blood cultures
Serum save
Stool for virology
Throat swab for bacteriology/virology
Blood for PCR (2x EDTA tubes)

Cellulitis:
Blood cultures
Skin swab
Serum save

Fever from Abroad:
Malaria film
Serum save
Blood cultures
Other samples as indicated (urine, T/S etc)

Malaria:
Malarial film on FBC
Clotting screen
CXR
ECG
Group and Save
Lactate/glucose (grey glucose tube)

Early morning Urine samples for AFB culture:

- Three EMUs should be sent from patients with suspected urogenital or intrabdominal TB.
- EMUs are sent from patients with suspected TB at other sites only if specifically requested by the doctors.
-

Haematology; Blood transfusion
Remember to avoid giving CMV+ blood to CMV IgG -ve HIV-infected patients.

2.5. ISOLATION

Primary source of recommendation, Local guidelines:
http://stginet/Policies/Clin_2-InfCon/Clin_2Home.aspx

National / International Guidelines:
FP3 standard masks, see HSE guidelines:
http://www.hse.gov.uk/news/2009/facemasks.htm

Points

- Use alcohol gel before and after patient encounters.
- Always think what type of bed the patient requires.
- Patients with diarrhoea or possible TB must be isolated in a side-room.
- On McEntee all beds are negative pressure – do **not** use for neutropaenic patients.
- Ruth Myles Unit rooms are positive pressure – do **not** use for patients with transmissible infections.
- For suspected drug resistant TB, side-rooms 2 or 3 give a greater level of security (double doors / Hepa filtration).

2.5.1. Isolation Categories

Isolation Categories are designated by signs on the door – read instructions carefully:

Respiratory Isolation (Blue sign)
For patients who have an airborne infection e.g. Tuberculosis

- Masks must be worn at all times in the room

Source Isolation (Yellow sign)
Indicates that the patient may have a disease that can be transmitted by direct contact. e.g. MRSA

- Gloves and aprons must be worn at all times

Source Isolation with Mask (Light blue sign)

- Gloves, aprons and masks must be worn at all times

Protective Isolation (White sign)
For patients who have a weakened immune system

- Aprons must be worn and hands washed thoroughly before entering the room

Protective clothing
Protective clothing (gowns, gloves, aprons, masks and overshoes) are provided.
Trust policy states that **EYE PROTECTION** (stored in Treatment room and sluice) and **GLOVES** must be worn at all times when handling body fluids or carrying out procedures e.g. phlebotomy, lumbar puncture, etc.

Isolation of Patients with Tuberculosis – see 8.7

2.6. NOTIFICATION

We have a duty to notify the following diseases under the Health Protection (Notification) Regulations 2010:
https://www.gov.uk/notifiable-diseases-and-causative-organisms-how-to-report

The notification book is kept on the ward, but the form is also at:
https://www.gov.uk/government/publications/notifiable-diseases-form-for-registered-medical-practitioners

Urgent cases (e.g. Meningococcal meningitis) should be notified to the SWL Health Protection Team on 0344 326 2052 (Fax: 0344 326 7255) – this is a 24/7 number.
Enquiries regarding rabies management go straight to Colindale: 0208 327 6204.

Acute encephalitis
Acute infectious hepatitis
Acute meningitis
Acute poliomyelitis
Anthrax
Botulism
Brucellosis
Cholera
Diphtheria
Enteric fever (typhoid or paratyphoid fever)
Food poisoning
Haemolytic uraemic syndrome (HUS)
Infectious bloody diarrhoea
Invasive group A streptococcal disease
Legionnaires' disease
Leprosy
Malaria
Measles
Meningococcal septicaemia
Mumps
Plague
Rabies
Rubella
Severe Acute Respiratory Syndrome (SARS)
Scarlet fever
Smallpox
Tetanus
Tuberculosis
Typhus
Viral haemorrhagic fever (VHF)
Whooping cough
Yellow fever

Report ***other diseases that may present significant risk to human health*** under the category 'other significant disease'.
HIV notification is performed by the HIV Clinical Nurse Specialist (Ext 2690 or Bleep 6315)

2.7. DISCHARGES AND DEATHS

2.7.1 Discharge Summaries

To be done by SHO/CMT within 3 days of discharge.

Critical issues are **drugs on discharge** and **outstanding follow-up issues** to be addressed in clinic.

2.7.2 Deaths

- Inform GP as soon as possible – next working day
- Discuss PM (especially HIV) with SpR and consultant
- In general, we avoid putting "HIV" or "AIDS" on the death certificate but tick the "Further information..." box in HIV cases

2.8. PERSONNEL AND CONTACTS

Matron:
Linda Smith, matron CIU/GUM: ext 0342 / bleep 7562

Consultants:
Dr Amber Arnold (AA)
Dr Tihana Bicanic (TB)
Dr Catherine Cosgrove (CC)
Prof. Tom Harrison (TH)
Dr Angela Houston (AH)
Prof. Derek Macallan (DM)

On wards on a rotating basis. OPD sessions for HIV and general ID as above.

Consultant	Contact number
TB	Ext 2911
CC	Ext 3474
TH	Ext 0447 / bleep 6706
AH/AA	Ext 5673
DM	Ext 0283 / aircall SG 928
Dept Secretaries:	Wanda Gardiner - 5829

Registrars:
Ward SpRs: bleep 6036 / 7166
Referrals: bleep 7568

Physician Associate
Louise Wooton – bleep 7101

SHOs:
bleep 6308 / 6216 / 6729

McEntee Ward:
Ward: ext 3280 / 3147
Sister: Georgina Couchman, Office ext 1306 or McEntee Ward
Receptionist: ext 3764

HIV specialist nurse:
Helen Webb: ext 2690 / bleep 6315

Pharmacy
In hours: bleep 6016; Courtyard Ext1803, or air call SG264

Clinics:
Courtyard Clinic Reception / HIV Notes: ext 3140
Courtyard Clinic Nurses: ext 2690

GUM (HIV) consultants:
Dr Bojana Dragovic: ext 0582
Dr Phillip Hay: ext 1656 / bleep 6505
Dr Aseel Hegazi: ext 4663
Dr Richard Lau: ext 3437 / bleep 6168
Dr Mark Pakianathan: ext 1652 / air call SG332
Dr Katia Prime: ext 0582
Dr Tariq Sadiq: ext 5740

Secretary to consultants: ext 3496 / 3355

Microbiology consultants:

Dr Aodhan Breathnach: ext 5735
Dr Meaghan Cotter: direct dial only: 020 8672 8297
Dr Angela Houston / Amber Arnold: ext 5673
Dr Matthew Laundy: ext 5678
Dr Tim Planche: ext 2683
Dr Cassie Pope, Consultant Clinical Scientist - Virology: ext 5734
Dr Peter Riley: ext 5707
Dr David Carrington – virology: ext 3267
Virology: ext 5686 & 5687

Secretary to consultants: ext 5674

3. PROTOCOLS FOR INFECTION EMERGENCIES

3.1. SEVERE RESPIRATORY ILLNESS

- Wear respiratory protection when taking samples (throat swab/induced sputum/NPA)
- Inform the virology department if you are suspecting an unusual respiratory pathogen.
    - New pathogens may not be picked up on routine testing; samples will need to be sent to Reference labs. Recent "new" pathogens have included MERS and SARS:

3.1.1 MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS (MERS-CoV)

Primary source of recommendation:
PHE: For MERS-CoV see:
https://www.gov.uk/government/publications/mers-cov-risk-assessment

National / International Guidelines:
WHO: latest update at time of press:
http://www.who.int/csr/disease/coronavirus_infections/en/
CDC: http://www.cdc.gov/coronavirus/mers/

3.1.2 SARS

Primary source of recommendation:
National / International Guidelines:
WHO: http://www.who.int/csr/sars/en/
CDC: http://www.cdc.gov/sars/index.html

Local guidelines:
http://stginet/Policies/Patient%20related/Infection_Control/Clin_2_0_AppD_Prot24.pdf

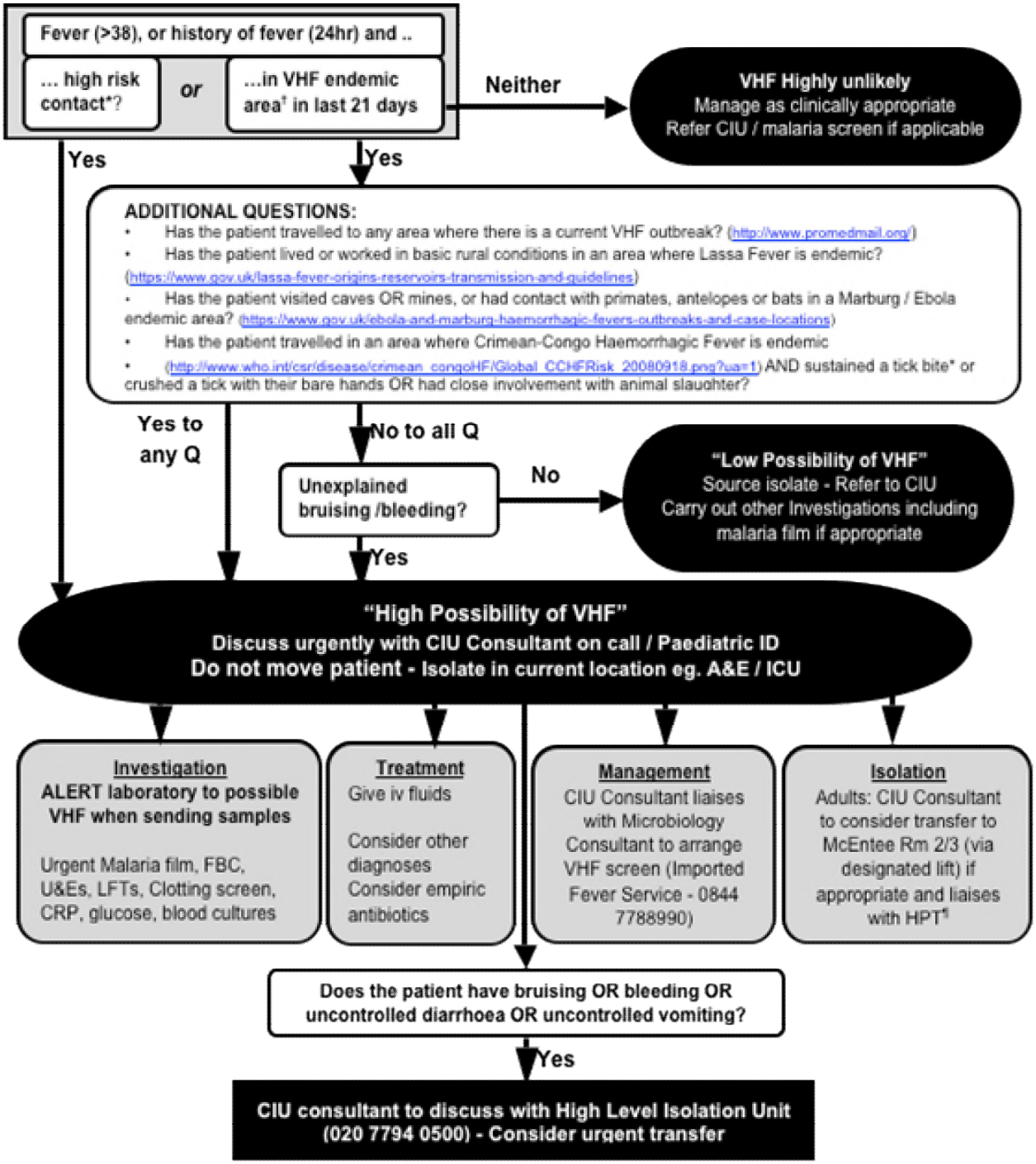
Points to Remember:

- SARS may have a long incubation and late presentation
- Dyspnoea may not be apparent in SARS
- NPA in a patient strongly suspected of SARS may be hazardous: use high efficiency mask

3.2. VIRAL HAEMORRHAGIC FEVER

See: https://www.gov.uk/government/publications/viral-haemorrhagic-fever-algorithm-and-guidance-on-management-of-patients

Operational application of guidelines within St George's NHS Healthcare Trust for immediate management of suspected cases:



Notes:

* **High risk contact** - Someone who has cared for / come into contact with body fluids of / handled clinical specimens (blood, urine, faeces, tissues, laboratory cultures) from an individual or laboratory animal known or strongly suspected to have VHF?

† (https://www.gov.uk/viral-haemorrhagic-fevers-origins-reservoirs-transmission-and-guidelines)

¶ SW London Health Protection Team - 0844 326 2052 (24 hrs)

3.3. DELIBERATE RELEASE OF BIOLOGICAL AGENTS

Primary source of recommendation:
Copy of Document: St George's Hospital Major Incident Plan – October 2007, Appx 3, page 143
http://stginet/Policies/Emergency/MajorIncidentPlan.doc

National / International Guidelines:
https://www.gov.uk/government/collections/deliberate-and-accidental-releases-investigation-and-management

See full recommendations, including helpful diagnostic illustrations, in Major Incident Plan as above (page 143).

3.3.1. Early recognition and management

If deliberate release of a biological agent, or any of the conditions described below are suspected, it must be discussed with senior staff - the CIU Consultant and the senior doctor in A&E (Consultant / Registrar). They will ensure liaison with the on-call Microbiologist & CCDC as appropriate. The CCDC will then liaise with the Regional Epidemiologist, CDSC and the Police, if necessary.

3.3.2. Isolation of patients and safety of staff

Some of the infections mentioned below (especially Smallpox and Plague) will be highly infectious to staff, including laboratory staff, and other patients. As the true nature of these infections is unlikely to be recognised immediately, all patients with fever and a rash (especially a vesicular rash) should be isolated immediately in a single room. If there is serious concern that the rash is variola, staff should consider using eye protection and dust-mist masks, and should contact CIU/Microbiology URGENTLY to make a rapid diagnosis. In the meantime they should consider switching off the ventilation in the room, as the ventilation may spread the infection around A&E.

Similarly it is desirable to isolate all patients with severe acute respiratory illness, though it is realised that this may not be feasible in every case, given the high number of patients admitted with pneumonia, influenza, etc.

Clinical samples also pose a hazard to staff (including lab staff) – see notes below

3.3.3. Specific clinical syndromes that should arouse suspicion

Several illnesses are extremely rare in the UK (or officially eradicated, in the case of smallpox), and even one case should arouse suspicion of deliberate release. It is important to try to make the diagnosis as early as possible. There are certain clinical syndromes that suggest these illnesses, but remember that most people with these syndromes will turn out to have a 'benign' infection. Nonetheless, it is important to consider and exclude more sinister diagnoses at an early stage.

Syndrome	Possible cause	Notes
Sepsis with a **widened mediastinum** on CXR, but relatively clear lung fields.	Consider **Anthrax** (inhalational form)	
Sepsis: fulminant, with severe **pneumonia/DIC**, and possibly enlarged neck/axillary/groin nodes (**buboes**)	Consider **Plague**	In practice, this is unlikely to be distinguished from other causes of sepsis until results of blood cultures are known.
Neurological Illness: • **Descending** flaccid paralysis • Cranial nerve lesions • Absence of sensory loss • Fever • Respiratory paralysis • Normal CSF/CT scan	Consider **Botulism**	Likely to be confused with: • Stroke (often asymmetrical) • Guillain-Barré (ascending sensory loss) • Myasthenia gravis • CNS tumour or infection • Intoxication • Psychiatric illness
Skin Lesion: single, typically on arms, face, neck, trunk - surrounding **oedema, erythema & vesicles** - **central necrotic patch** - associated with fever & sepsis	• Consider **Anthrax** (cutaneous form)	Differential includes: • Ischaemia • Necrotising fasciitis • Cowpox
Vesicular rash with: • Severe prodrome (2-3 days): prostration, myalgia, rigors, vomiting, abdominal pain or confusion • Lesions deep in skin • Lesions are dense on the head and peripheries, >5 spots on any palm or sole • Lesions in any body area are at same stage of development • Lesions evolve slowly: • Day 1-2: macules • Day 2-4: papules • Day 5-12: vesicles and then pustules • **Patient has had previous Chicken pox**	Consider **Smallpox (Variola)**. **Chicken pox** remains the most common cause of a generalised vesicular rash: Chicken pox patients are less ill, with no PHx of chickenpox; lesions occur in crops every couple of days, lesions are superficial, small and watery. **Enteroviruses** (including **Coxsackie viruses** & **Echoviruses**) are also common causes of vesicular rashes	• Every patient with a **rash and fever** should be **isolated in a single room** in A&E, irrespective of the perceived risk of smallpox **Refer urgently if:** (i) a definite previous history of chickenpox OR (ii) unusually severe cases OR (iii) cases with >2 of the typical features of variola **Isolate the patient** and **minimise further exposure** of staff to patient; consider the need to wear high-efficiency masks and eye protection; consider switching off ventilation in room.

3.3.4. Investigation of possible deliberate release

The following is a generic guide, but the final choice depends on the presenting features. Tests marked should be sent from all patients with unusual severe illness, outbreaks or suspected deliberate release.

Samples may pose a hazard to staff – use strict universal precautions during collection, **warn the laboratory**, label the samples and request cards '**High Risk**', and seal carefully before sending.

The **chute system should NOT be used** for such samples – they may be lost, or may break and contaminate the system. They must be hand-delivered to the lab.

Microbiological:

- **Blood cultures**: should be sent from all febrile/septic patients, before antibiotics if at all possible, whether or not deliberate release is suspected. Send at least one set, preferably two sets**.**

- **Serum**: 2 x 10mls clotted blood (Gold top) for serology and biological toxin assays

- **Whole blood: several** EDTA tubes for PCR or other molecular investigations

- **Urine**: > 20mls in a normal sterile container for standard testing & **storage**

Other tests to consider:

- Sputum/BAL/Endotracheal aspirate
- Nose & throat swabs
- Pus; swab of any local lesions
- Vesicle fluid in viral transport medium and/or dried onto slide
- Biopsy tissues from any local lesions/abscess/necrosis split between Micro (**not** formalinised) and Histo
- Faeces
- CSF, pericardial fluid, pleural fluid
- Any suspect food

Toxicological:

When dealing with an unusual illness of unknown aetiology, take samples for toxicology: it may not be necessary to examine all the samples if the diagnosis later becomes clear. Bottles for toxicological screens are held in 'Toxi-Boxes' in A&E.

Send: 10ml blood in plastic lithium-heparin tube
5ml blood in glass lithium-heparin tube
4ml blood in EDTA tube
30ml urine – no preservative
(smaller volumes in children)

4. POST-EXPOSURE PROPHYLAXIS (PEP) FOR BLOOD-BORNE VIRUSES

Primary source of recommendation: ICT

Local Guidelines:
Appendix D - Protocol 7 - Universal Precautions for the Prevention of Occupational Exposure to Blood-borne Viruses at: http://stginet/Policies/Clin_2-InfCon/Clin_2Home.aspx
Sharps policy: http://stginet/Policies/Clin_2-InfCon/Clin_2_06.pdf
PEP for HIV:
http://stginet/Publications/Clinical%20Publications/Grey%20book/HIV%20post%20exposure%20prophylaxis.pdf

National / International Guidelines:
HIV post-exposure prophylaxis: guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS – *updated 2008*
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_088185
United States guidelines-2005: http://aidsinfo.nih.gov/contentfiles/HealthCareOccupExpoGL.pdf

4.1. INTRODUCTION – RISK OF ACQUISITION OF HIV FOR EXPOSURE

Estimated per-act risk for acquisition of HIV, by exposure route*:

Exposure route	Risk per 10,000 exposure to an infected source
Blood transfusion	9,000
Needle-sharing injection-drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Receptive oral intercourse	1
Insertive oral intercourse	0.5

* assuming no condom use for risks from sexual exposures

Primary source of recommendation:
Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, CDC, Atlanta, Georgia : http://aidsinfo.nih.gov/contentfiles/NonOccupationalExposureGL.pdf

National Guidelines:
BASHH Guideline: UK Guideline for the use of post-exposure prophylaxis for HIV following sexual exposure. International Journal of STD & AIDS 2006; 17: 81–92
http://www.bashh.org/documents/58/58.pdf

4.2. ACTION FOLLOWING NEEDLESTICK INJURY/ CONTAMINATION

Local guidelines
http://stginet/Procedural%20Documents/Patient%20related/Infection_Control/Clin_2_6%20Sharps.pdf and Appendix 8 in the Grey book
National / International Guidelines:
HIV post-exposure prophylaxis. Guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS. DoH 2008
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_088185

The following is an extract from local guidelines

Following a NSI or contamination incident the following steps must be followed:

Act Immediately:

- Wash area liberally with soap and running water without scrubbing
- Do not use antiseptic or strong detergent washes
- Allow natural bleeding, do not suck wounds
- Cover with waterproof plaster
- Rinse eyes with water before and after removal of contact lenses
- Clean contact lenses with normal lens cleaning solution.

Report:

- Contact OHD by bleep 8092
- Out of hours attend the A&E and ask for immediate attention (Do not wait for triage)
- Complete an adverse incident form
- If the injury is reported to A&E during out of hours, to contact OHD as soon as it opens to complete risk assessment and follow up.

Risk Assess:

- Normally this is done by OHD/ A&E staff, but you may be asked for advice
- Source testing should be sought:

4.2.1 Guidelines for obtaining source patient's blood in sharps Injuries

- All source patients must be tested for HBV,HCV & HIV to comply with Department of Health recommendations. This helps prevent discrimination of individual patients
- Be carried out by a member of the clinical team **other than the injured worker** caring for the patient
- Be based on an informed consent obtained explaining the reason that it would assist in the safe provision of effective PEP to the injured staff member.
- Agree the method of informing the results to the source patient at the time of obtaining consent. Inform that If the source patient is positive for one of the BBV, they would be counselled and referral made to the Clinical Infection Unit
- Irrespective to the risk status to BBV carriage, proceed to testing. Inform source patient that results will be made available to OHD and the recipient of sharp injury
- If a positive result is obtained from a source patient, liaise with Consultant Virologist and Clinical Infection Unit for advice on further management. The test would be normally repeated before further action is taken.
- In the case of a true positive result there are many advantages to the diagnosis being known, both to the individual and to their contacts
- Where it is not possible to obtain informed consent, e.g. refusal or confused /unconscious patient, ensure recipient is managed with available information. In the case of a deceased patient, do not request a blood test for BBVs but discuss with Consultant OH Physician or Consultant Virologist.
- Address the issue of 'window period' due to ongoing risk in the source patient at the time of consent. A decision on a repeat test of the source patient and continuing with PEP of the staff member should be based on likelihood of 'window period' where the source may be infectious but the tests used are not sensitive to diagnose this at the time of injury.

4.2.2 Immediate risk assessment and the criteria for prescribing PEP for HIV

PEP should be recommended to healthcare workers if they have been exposed to blood or other high risk body fluids. If the injury must meet all three criteria listed below to recommend immediate PEP:

- high risk fluid was involved in the injury
- significant exposure as a result of the injury
- Source patient is classified as high risk

The details of each criterion are outlined below.(HCWs should not be offered PEP following contact through any route with low risk materials (e.g. urine, vomit, saliva, faeces) unless they are visibly blood stained.)

<table>
<tr><th colspan="3">High Risk body fluids</th></tr>
<tr><td colspan="2">• amniotic fluid
• vaginal secretions
• semen
• breast milk
• CSF
• peritoneal fluid
• pericardial fluid
• synovial fluid
• saliva in association with dentistry
• unfixed tissues and organs</td><td>The following fluids had to be visibly blood stained to be treated as high risk fluid:
• urine
• saliva
• sputum
• faeces
• vomit</td></tr>
<tr><th colspan="3">Significant exposure as a result of the injury</th></tr>
<tr><th>Percutaneous injury</th><th>Mucous membrane exposure</th><th>Exposure over broken skin</th></tr>
<tr><td>Skin pierced with a
• solid needle
• blunt instruments
• a hollow needle or
• a sharp instrument such as a blade or a scalpel

bone fragments</td><td>High risk body fluids in contact with HCW/ injured persons broken skin such as:
• fresh cuts or abrasions which are less than 24 hrs old
• active eczema etc</td><td>High risk body fluids in contact with eyes or inside of mouth or nose</td></tr>
<tr><th colspan="3">High risk factors in the source patients</th></tr>
<tr><td colspan="3">• Source patient HIV positive
• If HIV status is unknown, risk for HIV as follows
• Possible HIV related illnesses
• Homosexual/bisexual man and unsafe sex
• IVDU & needle sharing
• Native of Sub Sahara Africa or S.E Asia
• Prisoner
• Prostitute
• Or partners of the above</td></tr>
</table>

4.2.3 Starting prophylaxis

Don't forget to consider Drug Resistance, allergy, pregnancy, drug-interactions.

As current thinking recommends that treatment should be **started ideally within 1 hour** of the incident, **standard PEP** should be given immediately based on available information pending further evaluation. It should not be delayed for concern on possible drug resistance or testing of source patients which will take more than one hour. The standard regime in the emergency pack is also used during pregnancy if the risk is significantly high (known HIV positive source) and should be recommended.

Further guidance can be obtained from the Consultant in Occupational Medicine or medical deputy or the on call Clinical Information Unit (CIU) consultant (if out of hours).

- Ensure that the individual receives a copy of Advice for Exposed Staff on the Use of Antiviral Drugs. This leaflet is kept together with the emergency packs of medication on McEntee, in the Courtyard Clinic, in Occupational Health and in Accident and Emergency.

- Based on risk assessment as outlined in section 6.5.1, write an outpatient prescription, as shown below and give the emergency pack to injured staff member:

Truvada	***one tablet once daily***	***)***	***5 days supply***
Raltegravir 400mg	***one tablet <u>twice</u> daily***	***)***	***5 days supply***

- **Ensure a referral is made to OHD on the next full working day.**

The final decision whether to start prophylaxis must be made by the individual after full discussion. Once PEP is started, it will be reviewed by the Consultant in Occupational Medicine. The member of staff has the option of starting treatment prophylaxis immediately and then stopping it after full discussion with the duty CIU consultant or the Consultant in Occupational Medicine on the next working day. The online Cohort2008 form must be completed.

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4.2.4 Post exposure prophylaxis: Discussion with the exposed member of staff

The individual should be informed that the Expert Advisory Group on AIDS (EAGA) appointed by Department of Health has produced guidance on the current recommended regime for post-exposure prophylaxis. Aspects that should be included and considered in the discussion include:

- The risk of becoming infected is low and the overall risk for occupational percutaneous exposure to HIV infected blood is about 3 per 1,000 injuries. The risk of acquiring HIV through mucous membrane exposure is less than 1 in 1,000, e.g. eye splash. This will be higher if the source has a high viral load or the exposure is heavy.
- The recommendation from the DoH's guidance is that if treatment is to be taken, it should be started quickly, i.e. within 1 hour of the incident wherever possible. The drugs should be considered for use for up to 72 hours following exposure.
- Available information support the use of the standard regime used in PEP in pregnancy but it should be restricted to high risk injuries only.
- Adequate barrier contraceptives should be used to prevent pregnancy and to protect the partner during treatment until HIV testing is complete.
- Blood/semen/tissue donation should be avoided until the outcome of the incident is known.
- Side effects are quite common. They include nausea, headache, fatigue, loss of appetite and vomiting. Anaemia and leukopaenia are rare in otherwise healthy individuals. Lamivudine has been reported to cause pancreatitis and Kaletra may cause diarrhoea. Drug induced hepatitis may occur although is rare. Gastrointestinal side effects may be mitigated by drinking five litres of water per day. It is usual for side effects to cease on stopping medication.
- Advice should, however, be given to reinforce the importance of infection control measures, safer sex and avoiding blood donation during the follow-up period. This position reflects a judgement that the risk to the health care worker of becoming infected may both be high enough to justify taking PEP and engaging in safer sex but remote enough not to warrant modification of work.

Because these are new drugs used only in people who are already HIV positive, little is known about their side effects in combination when given short term to staff without HIV infection. The safety profile of the drugs are carefully considered by the EAGA and reviewed regularly, However, there is always uncertainty of the unknown safety risk in short and long term. Therefore it should only be used when there is a significant risk of HIV transmission.

- The prophylaxis course will usually last for 4 weeks.
- The individual will need monitoring i.e. blood tests, whether or not they take PEP.
- Any acute febrile illness which occurs in the 3 months following the incident should be reported.

4.2.5 Follow up arrangement for inoculation incidents

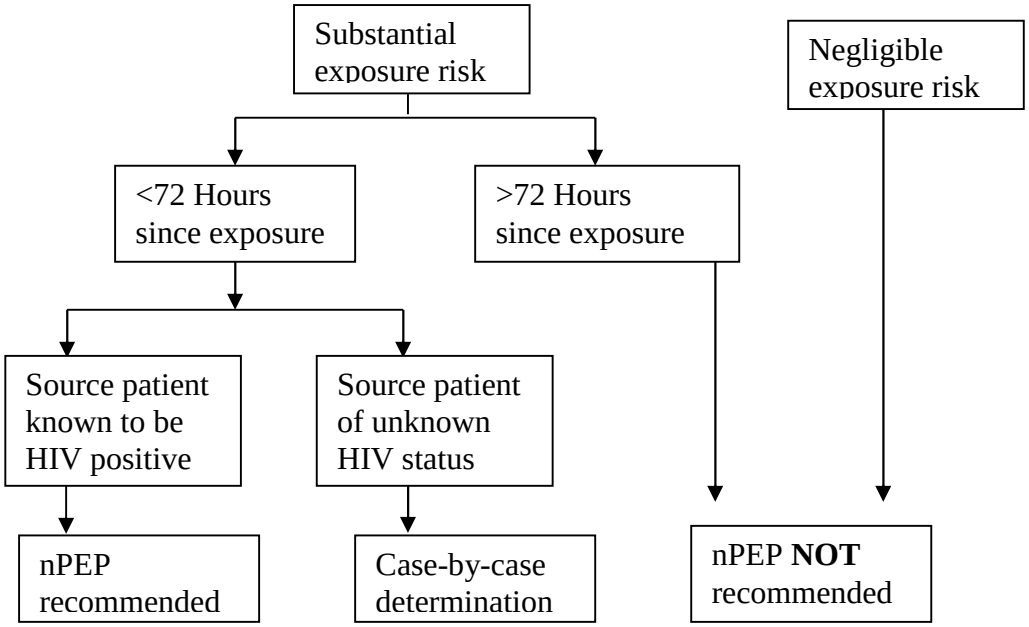
All staff in the following categories must attend for follow up testing as advised by OHD:

- Staff who had an injury from a source patient with a known infection with BBV
- Testing of source patient was not possible (for whatever the reason)
- An unknown source

4.3. PEP FOLLOWING SEXUAL EXPOSURE TO HIV (PEP-SE)

Primary source of recommendation:
Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Non-occupational Exposure to HIV in the United States. MMWR (Recommendations and Reports) Jan 2005; 54(RR02):1-20 http://aidsinfo.nih.gov/contentfiles/NonOccupationalExposureGL.pdf
Local Guidelines
National / International Guidelines:
BASHH Guideline: UK Guideline for the use of post-exposure prophylaxis for HIV following sexual exposure. International Journal of STD & AIDS 2006; 17: 81–92
http://www.bashh.org/documents/58/58.pdf
BHIVA:
http://www.bhiva.org/PEPSE-guidelines.aspx
http://www.bhiva.org/documents/Guidelines/PEPSE/PEPSE2011.pdf

CDC (US) Algorithm for Evaluation and Treatment of Possible Nonoccupational HIV exposures



Substantial Risk for HIV Exposure

Exposure of
Vagina, rectum, eye, mouth or other mucous membrane, nonintact skin, or percutaneous contact

With
Blood, semen, vaginal secretions, Rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood

When
The source is known to be HIV-infected

Negligible Risk for HIV Exposure

Exposure of
Vagina, rectum, eye, mouth or other mucous membrane, intact or non-intact skin, or percutaneous contact

With
Urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood

Regardless
Of the known or suspected HIV status of the source

Referrals for PEP-SE
Referrals for PEP-SE during working hours should immediately be diverted to the Health advisors at the Courtyard Clinic:

Extension: 3342 (020 8725 3342)
Alternative number: 020 8725 4999

If patients present outside working hours the algorithm above should be followed in discussion with the CIU Consultant on call. All patients (whether given PEP-SE or not) should be referred to the health advisors in Courtyard Clinic the next working day for follow-up.

For borderline cases, or if uncertainty exists about whether PEP-SE should be prescribed or not, it is reasonable to give a starter pack (as for occupational health) and refer to Health advisors in GUM for the next working day.

Baseline bloods (except HIV antibody testing) should be taken as for occupational exposure from all patients prescribed PEP-SE.
HIV antibody tests should preferably be done in the GUM clinic the next working day.
Potential source patients if attending with patients should also be referred to the GUM clinic.

Risk that source is HIV positive from BASSH 2006 guideline

Community group	**HIV seroprevalence**	
Homosexual men*		
London	20.3%	
Scotland	3.2%	
Elsewhere	3.6%	
Heterosexuals**	Male	Female
UK	0.5%	0.2%
Rest of Europe	2%	0.2%
North America	2.9%	0.1%
Cental and South America	2.4%	0.9%
Australasia	0.8%	0.1%
Caribbean	1.2%	1.0%
Sub Saharan Africa	6.9%	11.3%
South Asia	0.5%	0.6%
East and South East Asia	0.5%	0.7%
N. Africa and Middle East	0.5%	0.4%
Injecting drug users*		
London	2.9%	
Elsewhere in the UK	0.5%	

*HPA data 2004

** HPA data 2004. For more info re prevalence rates for exposures outside of the UK or for individuals recently moved to the UK can be obtained at www.unaids.org

5. ANTIRETROVIRALS IN TREATMENT OF HIV-POSITIVE ADULTS

5.1. INTRODUCTION - THE PURPOSE OF THESE GUIDELINES

Prescriber Restriction

Within the Trust, antiretroviral drugs are restricted to use by Clinical Infection Unit, GU Medicine and Paediatric Infectious Diseases doctors only

Except for: 1. Post-exposure prophylaxis by A&E in consultation with Staff Health
2. Use in pregnancy by Obs & Gynae only in consultation with CIU/GUM

These guidelines have been developed in accordance with the British HIV Association (BHIVA) and London LSCG Guidelines, combined with local practice. They should be interpreted and applied in consultation with the local ARV advice group which meets weekly.

Primary sources of recommendation:
Product SPC's
http://www.medicines.org.uk/emc/

Local Guidelines:

National / International Guidelines:
See BNF, THE SANFORD GUIDE TO HIV/AIDS THERAPY,
BHIVA Guidelines updated 2016
http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf

5.2. ANTIRETROVIRAL DRUGS: DOSES, REGIMENS & GUIDANCE

Rarely used drugs (including non-EC and EC Didanosine, Stavudine and Delavirdine (unlicenced)) are not included in these Tables

INDIVIDUAL AGENTS: Nucleoside/Nucleotide analogue Reverse Transcriptase Inhibitors (NRTIs)

APPROVED NAME	**ABACAVIR**	**EMTRICITABINE**	**LAMIVUDINE**	**TENOFOVIR DISOPROXIL FUMARATE**	**ZIDOVUDINE**
Commonly used Abbreviation	ABC	FTC	3TC	TDF	AZT
Brand Name	Ziagen®	Emtriva®	Epivir® Generic brand available	Viread®	Retrovir® Generic brand available
Formulation Available*	300mg tablets 20mg/mL Liquid	200 mg capsule 10mg/ml Liquid *Note: 240mg oral solution = 200mg capsule*	100mg tablets 150mg tablets 300mg tablets 50mg/5ml Liquid	245mg tablets 33 mg/g granules (with 1 gram scope) *Note: 7.5 scoops of granules ~ 245mg tablet*	100mg & 250mg capsules 50mg/5mL Liquid 10mg/mL injection
Usual Dosing	300mg bd	200mg od (capsule) 240mg od (liquid)	150mg bd	245mg od	250mg bd
Alternative Dosing	600mg od	-	300mg od	-	200mg tds (2x100mg tds)
Additional information	*Swallow whole with water* *At start of therapy counsel about recognition of* ***hypersensitivity*** *and that symptoms vary between individuals*	*May open capsules and mixed with water*		*Tablet can be crushed and dissolved in water* *Mix 1 scoop of granules with 1 tablespoon of soft food (yogurt) and take immediately without chewing. Do* ***not*** *mix granules with liquid and should be taken with food*	*May open capsules and mix with food or cool tap water* *N & V may be reduced if taken with food*

FIXED DOSE COMBINATION: NRTIs

APPROVED NAME	ABACAVIR + LAMIVUDINE	EMTRICITABINE + TENOFOVIR DISOPROXIL FUMARATE	EMTRICITABINE + **T**ENOFOVIR **A**LAFENAMIDE **F**UMARATE (TAF)[1]	
Brand Name	**KIVEXA®** Generic brand available	**TRUVADA®** (TVD)	**DESCOVY® [2]** 200MG**/10MG***	**DESCOVY® [2]** 200MG**/25MG***
Usual Dosing	One tablet daily	One tablet daily	One tablet daily	
	One tablet contains 600mg abacavir and 300mg lamivudine	One tablet contains 245mg tenofovir disoproxil and 200mg emtricitabine	One tablet contains 200mg emtricitabine and 10mg tenofovir alafenamide	One tablet contains 200mg emtricitabine and 25mg tenofovir alafenamide
Additional information for healthcare professionals and patients	*Tablet may be split or crushed* *At start of therapy counsel about recognition of* ***hypersensitivity*** *and that symptoms vary between individuals*	*Best absorbed with food* ***Swallowing difficulties:*** *may disperse tablet in half glass of water, orange juice or grape juice (may taste bitter)*	*Swallow whole with water* *The film-coated tablet should not be chewed, crushed, or split*	

1.Note: **TENOFOVIR ALAFENAMIDE (as fumarate)** is not available as a separate component.

2. *Each tablet of Descovy contains 200mg of emtricitabine and tenofovir alafenamide fumarate equivalent to either 10mg or 25mg of tenofovir alafenamide fumarate.

INDIVIDUAL AGENTS: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

APPROVED NAME	**EFAVIRENZ**	**RILPIVIRINE**	**ETRAVIRINE**	**NEVIRAPINE**
Common Abbreviation	EFV	RPV	ETR	NVP
Brand Name	Sustiva® Generic brand available	Edurant®	Intellence®	Viramune® Generic brand available
Formulation Available*	50mg, 100mg & 200mg capsules 600mg tablets *30 mg/mL Liquid has been discontinued*	25mg tablets	100mg tablets 200mg tablets	200mg tablets 100mg & 400mg MR tablets 50mg/5ml Liquid
Usual Dosing	600mg od	25mg od	200mg bd 400mg od (unlicensed)	200mg od for 14days then increase to 200mg bd or 400mg MR od
Additional information for healthcare professionals and patients	*Take on an empty stomach* *At first best to be taken at night to minimise CNS side effects, including : dizziness, insomnia, somnolence, impaired concentration, abnormal dreaming* *Counsel patients regarding **rash** within 2 weeks of starting therapy* *Can open capsules and mix powder with two teaspoons of either applesauce, grape jelly, yogurt or infant formula (but may result in hot "jalapeno" sensation)*	***Must be taken** with a 533kcal meal to obtain optimal absorption.* *Avoid PPI's.* *H_2-receptor antagonists at least 12 hours before or at least 4 hours after rilpivirine* *Avoid antacids at least 2hrs before or at least 4hrs after rilpivirine* *Treatment with rilpivirine resulted in an early small increase of mean serum creatinine levels which remained stable over time and is not considered clinically relevant.*	*After a meal* *Counsel patients regarding rash, usually in the second week of starting therapy. Appears more frequently in women.* ***Swallowing difficulties**: may disperse tablet in glass of water just before administration*	*MR tablets must swallow whole with water* *Can crush immediate release tablets & mix in water* *Counsel patients regarding rash usually in first 6 weeks and hypersensitivity* *Report new symptoms which may reflect hepatitis (nausea, vomiting, malaise, abdo pain) Nevirapine should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm3 or in adult males with CD4 cell counts greater than 400 cells/mm3, who have a detectable plasma HIV-1 RNA*

*Formulation: Please check Trust formulary for availability

SINGLE TABLET REGIMEN: NNRTIs

APPROVED NAME	TRUVADA® + EFAVIRENZ	TRUVADA® + RILPIVIRINE	DESCOVY25® + RILPIVIRINE
Brand Name	**ATRIPLA®**	**EVIPLERA®**	**ODEFSEY®**
Usual Dosing	One tablet daily	One tablet daily	One tablet daily
	one tablet contains: 245mg tenofovir disoproxil 200mg emtricitabine 600mg efavirenz	one tablet contains: 245mg tenofovir disoproxil 200mg emtricitabine 25mg rilpivirine	one tablet contains: 25mg tenofovir alafenamide 200mg emtricitabine 25mg rilpivirine
Additional information for healthcare professionals and patients	*Take on an empty stomach* *At first best to be taken at night to minimise CNS side effects, including : dizziness, insomnia, somnolence, impaired concentration, abnormal dreaming* *Counsel patients regarding **rash** within 2 weeks of starting therapy*	***Must be taken** with food (390kcaL) to obtain optimal absorption.* *Not to be taken with PPIs.* *H_2-receptor antagonists at least 12 hours before or at least 4 hours after Eviplera/Odefsey* *Avoid antacids at least 2hrs before or at least 4hrs after Eviplera/Odefsey* *The film-coated tablet should not be chewed, crushed or split.*	

<u>INDIVIDUAL AGENTS:</u> Protease Inhibitors (PIs)

APPROVED NAME	**ATAZANAVIR**	**DARUNAVIR**	**LOPINAVIR/r**
Brand Name	Reyataz®	Prezista®	Kaletra®
Formulation Available*	150mg, 200mg, 300mg capsules	75mg, 150mg, 400mg, 600mg, 800mg tablets 100mg/ml Liquid	Lopinavir 100mg/ritonavir 25mg paediatric tablet Lopinavir 200mg/ritonavir 50mg tablet Lopinavir 80mg/ritonavir 20mg per 1 ml Liquid
Usual dose(s) with boosting agent	300mg + Ritonavir 100mg or cobicistat 150mg DAILY	800mg + Ritonavir 100mg or cobicistat 150mg DAILY	2 x 200mg/50mg tablets twice a day
Alternative Dosing	Unboosted 400mg DAILY only under restrictive conditions. 400mg + Ritonavir 100mg DAILY during 2nd or 3rd trimester of pregnancy. Consider TDM	600mg + ritonavir 100mg BD in HIV-2, treatment experience, or during 2nd or 3rd trimester of pregnancy. Consider TDM	-
Additional information for healthcare professionals and patients	*Take with food or after meals* *Capsules maybe opened.* *Avoid PPIs.* *Antacids at least 1 hour before or at least 2 hours after atazanavir* *H_2-receptor antagonists at least 12 hours before or at least 4 hours after atazanavir*	*Swallow whole with water* *Take with food or after meals* *Counsel patients regarding **rash** within 4 weeks of starting therapy and resolves without stopping treatment.*	*Swallow whole with water* *Take with food or after meals* *Liquid to be kept in a refrigerator*

<u>FIXED DOSE COMBINATION:</u> Protease Inhibitors (PIs)

APPROVED NAME	**ATAZANAVIR + COBICISTAT** Fixed dose combination	**DARUNAVIR + COBICISTAT** Fixed dose combination
Brand Name	Evotaz®	Rezolsta®
Usual Dosing	One tablet daily	One tablet daily
	one tablet contains: 300mg Atazanavir 150mg Cobicistat	one tablet contains: 800mg Darunavir 150mg Cobicistat
Additional information for healthcare professionals and patients	*Swallow whole with water* *Take with food or after meals* *The film-coated tablet should be swallowed whole and must not be chewed, broken, cut or crushed* *Avoid PPIs.* *Antacids at least 1 hour before or at least 2 hours after Evotaz* *H_2-receptor antagonists at least 12 hours before or at least 4 hours after Evotaz*	*Swallow whole with water* *Take with food or after meals* *Counsel patients regarding **rash** within 4 weeks of starting therapy and resolves without stopping treatment.*

INDIVIDUAL AGENTS: Integrase Inhibitors (INIs)

APPROVED NAME	**RALTEGRAVIR**	**DOLUTEGRAVIR**
Brand Name	**Isentress®**	**Tivicay®**
Formulation Available*	400mg film-coated tablet	50mg tablet
Usual Dosing	400mg bd	50mg od
Alternative Dosing	-	50mg bd ➢ if resistance to other inhibitors of Integrase suspected ➢ Concomitant efavirenz, nevirapine, tipranavir or rifampicin
Additional information for healthcare professionals and patients	*Swallow whole with water* *At start of therapy counsel patients regarding* ***rash.*** *Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of ISENTRESS with aluminium and/or magnesium containing antacids is not recommended.*	*Tablet may be crushed* *Where there is indication for twice daily dosing, dolutegravir should preferably be taken with food to enhance exposure* *At start of therapy counsel about recognition of* ***hypersensitivity*** *– discontinue if any sign or symptoms develop* *Magnesium/ aluminium-containing antacid, iron and calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).* 10-14% decrease of creatinine clearance due to inhibition of renal transporters do not reflect a change in glomerular filtration rate

*Formulation: Please check Trust formulary for availability

SINGLE TABLET REGIMEN: INIs

APPROVED NAME	KIVEXA + DOLUTEGRAVIR	DESCOVY 10 + ELVITEGRAVIR/COBICISTAT	TRUVADA + ELVITEGRAVIR/COBICISTAT
Brand Name	**TRIUMEQ®**	**GENVOYA®**	**STRIBILD®**
Usual Dosing	One tablet daily	One tablet daily	One tablet daily
	one tablet contains: 600 mg of abacavir 300 mg of lamivudine 50 mg dolutegravir	one tablet contains 200 mg of emtricitabine 10 mg of tenofovir alafenamide 150 mg of elvitegravir, 150 mg of cobicistat,	one tablet contains: 200 mg of emtricitabine 245 mg of tenofovir disoproxil 150 mg of elvitegravir 150 mg of cobicistat
Additional information for healthcare professionals and patients	*Tablet may be crushed or split* *At start of therapy counsel about recognition of **hypersensitivity** and that symptoms vary between individuals* *Magnesium/ aluminium-containing antacids, calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of Triumeq (minimum 2 hours after or 6 hours before).*	*One tablet to be taken once daily with food.* *The film-coated tablet should not be chewed, crushed, or split.* *Separate Genvoya and magnesium/aluminium-containing antacid & multivitamin administration by at least 4 hours.*	*Swallow whole with water* *Take with food or after meals* *Avoid antacids 4hrs before or 4hrs after taking Stribild®* *Separate Stribild and magnesium/aluminium-containing antacid & multivitamin administration by at least 4 hours.* *Avoid in patients with CrCl < 70ml/min*

OTHER AGENTS:

	CCR5 BLOCKER *Only if tropism test shows CCR5-tropic*	**PHARMACOKINETIC ENHANCER (BOOSTING AGENTS FOR PROTEASE INHIBITORS)**	
APPROVED NAME	**MARAVIROC**	**COBICISTAT**	**RITONAVIR**
Brand Name	**Celsentri®**	**Tybost®**	**Norvir®**
Formulation Available *Please check Trust formulary for availability*	150mg tablet 300mg tablet	150mg tablet	100mg tablets 100mg powder for oral suspension
Usual dose	Standard dose: 300mg bd 150mg bd when co-administered with a potent inhibitor. A further reduction to 150mg od if CrCL <80 mL/min 600mg bd when co-administer with a potent inducer.	150mg od co-administered with ➢ Atazanavir 300 mg once daily or ➢ Darunavir 800 mg once daily	Co-administered in combination with other antiretroviral agents 100mg daily or twice a day depending on boosted agent
Alternative dose	Other off-label ONCE daily dosing with boosted PI has been used.	-	-
Additional information for healthcare professionals and patients	*Cutting or crushing tablet is not expected to negatively affect bioavailability.* *Can cause postural hypotension. Use in cautious for patients with antihypertensive medication, severe renal insufficiency and cardiovascular co—morbidities*	*Take with food or after meals* *Cobicistat can increase baseline creatinine up to 0.4 mg/dL (35 umol/L) due to inhibition of tubular secretion of creatinine.*	*100mg tablets* *Swallow tablet whole with water.* *Take with food* *100mg oral powder in sachets* *Pour on soft food (apple sauce or vanilla pudding) or mixed with liquid (water, chocolate milk, or infant formula).* *Refer to Package Leaflet for further information*

5.3. WHEN TO TREAT

Primary sources of recommendation:
BHIVA guidelines 2015 – 2016 update
National / International Guidelines:
BHIVA: http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf
Key References:
ACTG: http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0005575
START: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1506816
TEMPRANO: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1507198

TB-HIV co-infection guidelines:
http://www.bhiva.org/documents/Guidelines/TB/hiv_954_online_final.pdf

The aim of treatment is to extend the length and improve quality of life and reduce the risk of onward transmission through control of viraemia and reconstitution of the immune system, demonstrated by an increasing CD4 count.

5.3.1 Immediate versus delayed ART

Previously, starting treatment was delayed until the CD4 count had fallen to a predetermined level. We now effectively offer "immediate ART" to everyone. The evidence for immediate ART is based primarily on a large randomised control trial comparing immediate ART with ART deferred until the CD4 count was ≤350 cell/mm^3 (Lundgren et al., 2015; The TEMPRANO ANRS12136 Study Group 2015). Immediate ART reduced all cause morbidity and mortality by 57% and the risk of AIDS related morbidity and mortality by 72% relative to deferred ART. As a consequence of these data BHIVA, together with other international guidelines including WHO and EACS, recommend that **all HIV -1 positive patients be offered ART irrespective of CD4 count.**

The Clinical Commissioning Policy Proposition*: "Immediate Antiretroviral therapy for treatment of HIV-1 in adults and adolescents*" went out for public consultation on 7/7/2017. See:
https://www.engage.england.nhs.uk/consultation/commissioning-policy-antiretroviral-therapy/

5.3.2 Treatment as Prevention

NHS England already commissions *Treatment as Prevention* (TasP) (NHS England, 2015), enabling patients to **start ART at higher CD4 counts for the primary purpose of preventing the onward transmission of HIV.** All HIV positive individuals should be advised about the effectiveness of ART in preventing onward transmission and be offered ART for this purpose.

5.3.3 Primary HIV infections (PHI)

Patients diagnosed with primary HIV infections (PHI) - defined as HIV infection within a maximum of six months from the estimated time of HIV transmission- represent a special case in which **immediate antiretroviral therapy should be offered without delay**.

Patients with PHI with low initial CD4 T cell counts, high plasma viral loads (>100,000 copies HIV RNA) and short test intervals (diagnosis within 12 weeks of a previous negative test) have a more rapid rate of disease progression than others without these features. In the SPARTAC study, a post-hoc sub analysis showed the greatest benefit in those who started very soon after seroconversion, compared to those starting at ~6 months.

ART should be started as soon as possible for patients presenting with PHI with any of the following criteria, as these are known to be associated with morbidity or very rapid disease progression.

- **Neurological involvement**
- **Any AIDS-defining illness**
- **CD4 cell count <350 cells/µL**
- **PHI diagnosed within 12 weeks of a previous negative test**

Primary transmitted resistance currently occurs in about 6% individuals. Treatment in seroconversion has to be started before resistance assay and HLAB5701 results are ready.

Therefore start with

Truvada + Darunavir 800 mg and ritonavir 100 mg OD or

Truvada+ Rezolsta

in the absence of contra-indications to these agents.

Addition of an integrase inhibitor may be considered for rapid virological suppression. The Darunavir/ritonavir or Rezolsta can be stopped after 4 weeks if resistance assays for PI, RT and INSTI show wild type virus.

5.4. CHOICE OF INITIAL THERAPY

Primary sources of recommendation:
BHIVA guidelines 2015-16
http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf

Reference LSCG source
Key References:
UK resistance data: http://www.hivrdb.org.uk/hiv-drug-resistance-uk

Baseline assessment should precede choice of regimen, wherever possible, and include:

- Viral load
- Resistance assay
- HLA B*5701
- Hepatitis B serology

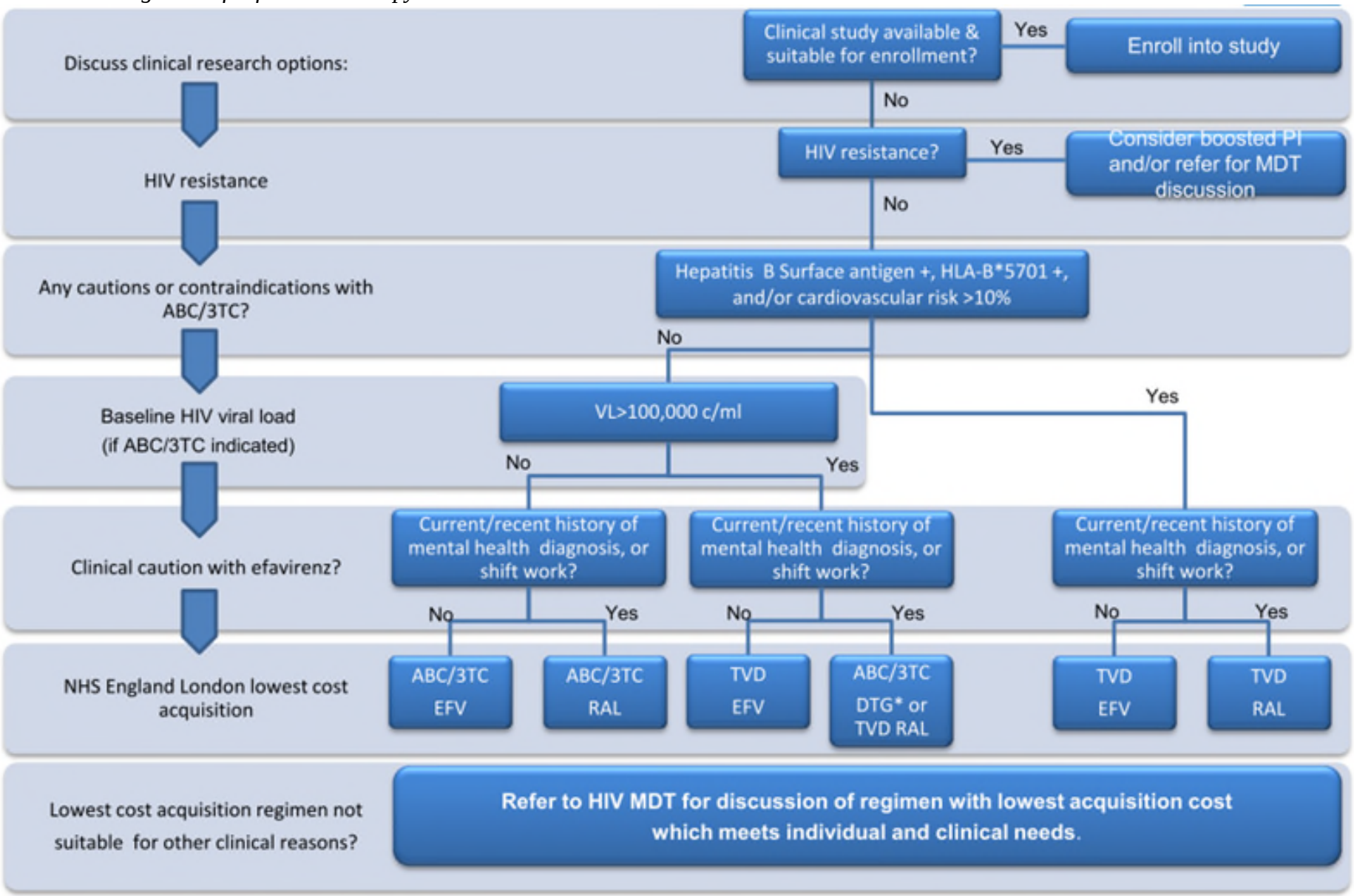
General approach to constructing a first-line regimen:

- Consider clinical trials as first option, if trials are recruiting for naïve patients
- Request a Pharmacy review pre-treatment
- Choice of nucleosides may be guided by:

HLA B*5701 positive	Do not use *abacavir* – increased risk of hypersensitivity
High Viral load (>100,000 /ml)	Avoid *abacavir/lamivudine (unless with dolutegravir)* and *Rilpivirine* – higher rates of virological failure
Pre-existing renal disease	Favours *abacavir or TAF-based therapy*
Co-existing Hepatitis B infection	Favours *tenofovir*
Pre-existing or high risk of CVD (>10% ten-year risk)	Avoid *abacavir*
Cost	Currently favours *abacavir/lamivudine*

First-line treatment recommendations for the London group should be followed:
Source: London Antiretroviral Therapy (ART) Prescribing Implementation Toolkit April 2017 NHS England

London ARV algorithm for first-line therapy



Notes

Preferred 1st line regimen where MDT approval not required unless specified:

- Generic abacavir/lamivudine + generic efavirenz or raltegravir
- Truvada (or Descovy* where clinically indicated) + generic efavirenz or raltegravir
- Atripla if clear clinical indication for a single tablet regimen (STR)
- Generic abacavir/lamivudine+ dolutegravir* (or Triumeq if clear clinical indication for STR)

  ***** *NHS England 'Commissioning policy for dolutegravir and Descovy' requires that MDT approval is obtained before use*.

- All other regimens are alternative and require MDT approval

KEY POINTS 1

First line therapy

- abacavir/lamivudine is the NRTI backbone of choice where clinically appropriate for patients starting ART.
- efavirenz is the preferred third agent unless there is a clinical contra-indication.

If there is a clinical indication to avoid, or to switch from efavirenz:

- Raltegravir should be considered initially in accordance with the algorithm
- Any need for once daily ART should be clinically driven and agreed by the MDT

In patients with baseline/transmitted drug resistance, or concerns regarding intermittent adherence, consider

- Evotaz, Rezolsta or ritonavir-boosted PI

KEY POINTS 2

-If there are potential adherence concerns with twice daily raltegravir:

- Referral to **MDT (Virtual Clinic)** should be made for all patients
- The foreseeable availability (Q3 20107) of raltegravir OD should be considered
- Consider 2NRTIs (preferably abacavir/lamivudine) with dolutegravir, rilpivirine, Evotaz, Rezolsta or Triumeq or Eviplera or Stribild
- Descovy, Odefsey or Genvoya may be considered where clinically indicated in place of Truvada, Eviplera and Stribild respectively.

Exceptional to efavirenz use

For patients stable on efavirenz based ART, a review of tolerability is recommended at all visits.

- No change to London DTSG 2011 guidance, other than BHIVA pregnancy guidelines now allows the use of efavirenz.
- Avoid efavirenz if depression/significant mental health issues or where side effects of efavirenz may have an impact on the work or lifestyle.

Raltegravir vs. alternative INIs

Although once daily combinations may be preferred for adherence/convenience, many patients would choose twice daily if it had fewer side effects or drug interactions.

- The lower price for twice-daily raltegravir means this is the **preferred alternative** when there are clinical indications to avoid efavirenz. Raltegravir should be used in preference to other options.

- A licensed, once daily formulation of raltegravir will be available from autumn 2017.
- Because of their higher price or national policy requirement for MDT approval dolutegravir, Triumeq, or Stribild (or Genvoya if clinically indicated) can only be used as a once-daily alternative to raltegravir **after referral to the MDT/Virtual Clinic.**

Caution with patients using supplements/antacids/multivitamins containing di or trivalent cations (e.g. Mg/Al/Ca/Zn/Fe) which may chelate raltegravir, dolutegravir or elvitegravir. Consult SPCs for raltegravir and all integrase inhibitors for advice

Single Tablet Regimens

Single Tablet Regimens (STRs) containing complete ART regimens should not be used unless there is cost parity to the equivalent multi-tablet regimen or there is a clear, clinical indication to use an STR as opposed to the individual components.

- With the availability of generic abacavir/lamivudine fixed-dose combination (FDC) from December 2016, and the preferential price for efavirenz and raltegravir, the use of STRs is not routinely indicated unless there is MDT/Virtual Clinic approval.
- Consideration should be given to switch patients on STRs to the NRTI FDC and appropriate 3rd agent.
- The lowest acquisition cost STR should be chosen for use.

Tenofovir alafenamide (TAF)

TAF may offer clinical benefit individuals with absolute or relative contra-indications to TDF where TDF-based therapy is preferred.

- TAF is available in 3 Fixed Dose Combinations:
  - Descovy: TAF/emtricitabine
  - Odefsey: TAF/emtricitabine/rilpivirine
  - Genvoya: TAF/emtricitabine/cobicistat/elvitegravir
- A commissioning policy for the use of Genvoya is available and has recently been extended to include the use of Descovy and Odefsey.
- All use of TAF-based products should be discussed in the MDT/Virtual Clinic and recorded in the patient records.

5.5. MONITORING THERAPY

Primary sources of recommendation:
National / International Guidelines / Key Reference:
http://www.bhiva.org/documents/Guidelines/Monitoring/2016-BHIVA-Monitoring-Guidelines.pdf

5.5.1. Monitoring for Efficacy

Clinical:

- development of new/recurrent opportunistic infections
- weight gain
- quality of life

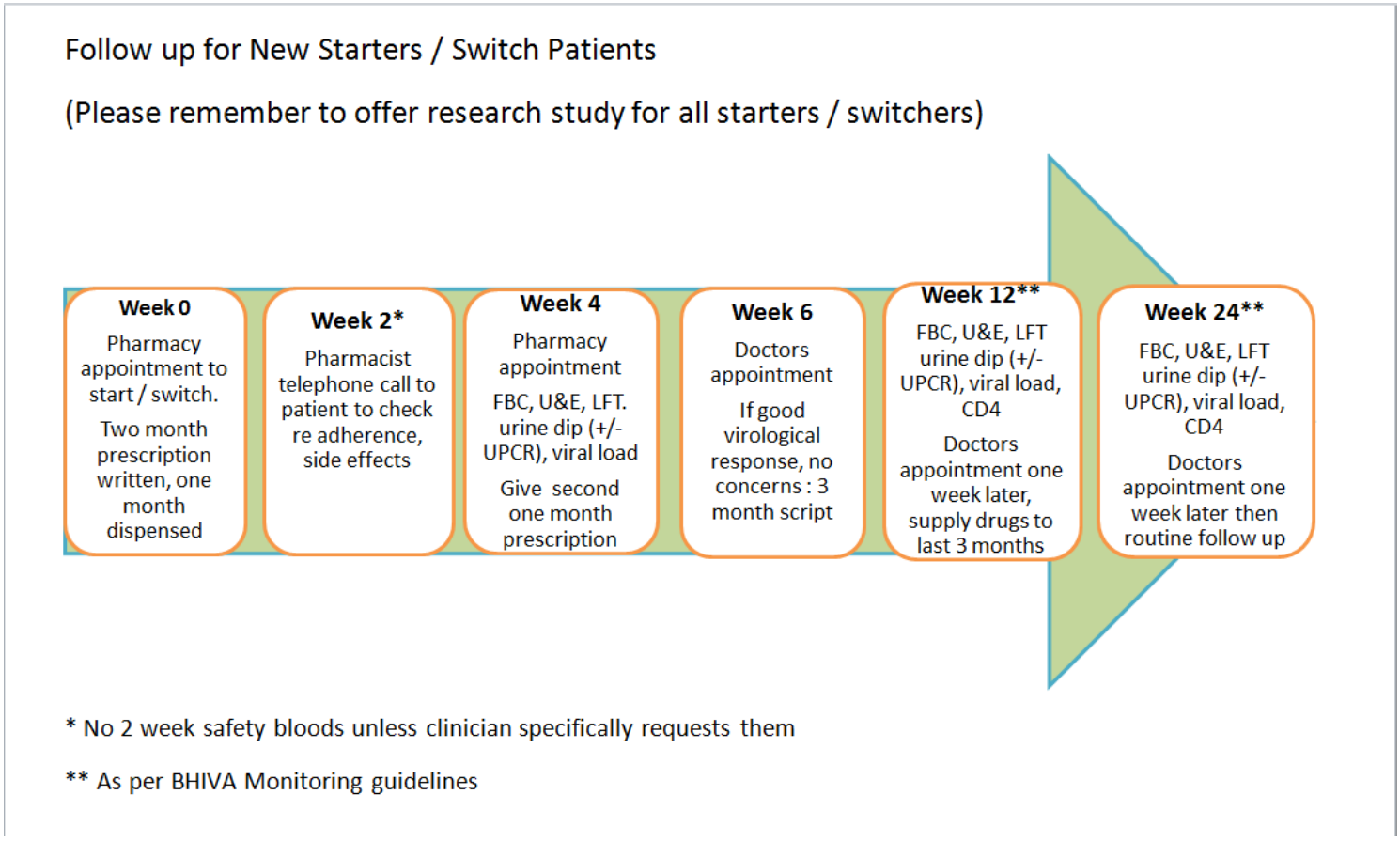
Virological:

- Viral load – baseline then after 1 month on treatment and again at 3 and 6 months then every 3-6 months thereafter using an ultra-sensitive assay
- Resistance testing – as below

Immunological:

- CD4 lymphocyte count – baseline then after 1 month on treatment, then every 3-6 months until >350, then yearly.

Courtyard Clinic monitoring pathway for New Starters / Switch patients



5.5.2. Resistance testing

Test for resistance in the following settings:

1. Newly diagnosed patients

Use the sample closest to the time of diagnosis - test at the time of initial presentation

2. Existing patients

a) Immediately prior to starting therapy

b) Suboptimal virological response to first-line therapy - minority species of resistant virus may be missed by conventional resistance testing at start of therapy

c) Virological failure

Notes on resistance testing:

- Routine resistance assays do not detect resistant viruses present at low levels (<20% of the total virus population).
- In the absence of drug pressure, the dominant virus population will revert to wild-type. Reversion is slower in transmitted resistance than in resistance selected by therapy.

5.5.3. Therapeutic drug monitoring (TDM)

TDM requests should be accompanied by the white form, as well as a blue microbiology form, including details of timing of last dose and timing of meal nearest last dose.

TDM is currently available for all protease inhibitors and efavirenz. On site TDM available for EFV, ATZ, lopinavir, ritonavir and raltegavir via the analytical unit (ASI ext 5345/2405). Nevirapine levels can be organised through Lab 21.

TDM is likely to be of little value for NRTIs as these agents require intracellular activation and levels of intracellular drug-triphosphate bear little relationship to plasma levels of the parent compound.

Rationale for Use of TDM (from BHIVA 2015)

TDM is **not recommended** for unselected use- however it may aid in the management of vulnerable populations or complex clinical situations.

E.g.

- Malabsorption
- Suspected drug interaction
- Suspected non-adherence
- Unusual or unlicensed dosing regimens such as once-daily boosted (LPV, SQV) or unboosted regimens
- Liver/renal impairment
- Pregnancy
- Children
- Patient with extremes of BMI

5.6. SIDE EFFECTS AND INTERACTIONS OF ANTIRETROVIRAL DRUGS

Primary sources of recommendation:
Product SPC's (see http://www.medicines.org.uk/)
Local Guidelines:
National / International Guidelines:
BHIVA http://www.bhiva.org/files/file1030835.pdf
For interactions: http://www.hiv-druginteractions.org/ and http://hivclinic.ca/drug-information/drug-interaction-tables/

5.6.1. Generic Drug Side-Effects

MHRA antiretroviral medicines: updated advice on body-fat changes and lactic acidosis 2015[1]
Consistent with current HIV treatment guidelines, product information will be amended to advise that weight gain and metabolic changes (such as lipid and glucose increases) may occur during treatment with any HIV medicine. However, these changes are partly linked to underlying disease control and lifestyle in addition to antiretroviral treatment. Warnings for lipoatrophy and lipoaccumulation will be retained only for zidovudine, stavudine, and didanosine
[1] https://www.gov.uk/drug-safety-update/antiretroviral-medicines-updated-advice-on-body-fat-changes-and-lactic-acidosis#summary

Fat redistribution and lipid disorders
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump). This is less common with the newer agents.
A higher risk of lipodystrophy has been associated with:

- Older age
- Longer duration of antiretroviral treatment
- Stavudine and zidovudine-containing regimens

Evaluation should include:

- Clinical examination for physical signs of fat redistribution
- Biochemical monitoring of fasting serum lipids and blood glucose (section 5.6.3)

Lipid disorders may require intervention.
Beware of interactions between statins and PIs in particular.

Hyperglycaemia
New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been reported in patients receiving protease inhibitors. Hyperglycaemia may be severe and may be associated with ketoacidosis.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia), and, in children exposed in utero, late-onset neurological disorders (hypertonia, convulsion, abnormal behaviour).

Hyperlactataemia and Lactic acidosis

Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis has been reported with the use of nucleoside reverse transcriptase inhibitors (NRTIs), generally after a few or several months of treatment.

Early symptoms of hyperlactataemia include:

- digestive symptoms - nausea, vomiting, abdominal pain
- non-specific malaise
- loss of appetite, weight loss
- respiratory symptoms (rapid and/or deep breathing)
- neurological symptoms (including motor weakness)

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, renal failure, or motor paralysis. If suspected, monitor closely and consider discontinuation of NRTIs.

High-risk groups include:

- obese women
- risk factors for liver disease (hepatomegaly, hepatitis, hepatic steatosis, use of hepatotoxic drugs and excess alcohol)
- co-infection with hepatitis C - treatment with alpha interferon and ribavirin

5.6.2. Laboratory Monitoring for Toxicity

FBC	Baseline, 2 weeks then monthly for 3 months, then yearly.
U&E, LFT, Glucose, Amylase	Baseline, 2 weeks then monthly for 3 months, then every 6 months
Lipid profile (fasting if possible)	Baseline, then every 12 months
CPK	3 monthly **only** if on AZT >6 months

Repeat more frequently if indicated by symptoms or if abnormal

Specific monitoring:

- Nevirapine therapy - check LFT every 2 weeks for first 2 months
- Muscle symptoms - check CPK
- Fatigue, myalgia etc. (symptoms of mitochondrial toxicity) - check lactate

There are many other potentially significant interactions – see www.hiv-druginteractions.org or http://hivclinic.ca/drug-information/drug-interaction-tables/

Particular care should be taken over the interactions with rifampicin or rifabutin in the treatment of mycobacterial disease. Most significant interactions are seen with NNRTIs and PIs. Please contact a pharmacist if you are in any doubt.

5.6.3 Interactions with Illegal/Recreational Drugs and Methadone

There are many other potentially significant interactions - Please refer to the Medicines Information/ward pharmacist or check the following resources:
www.hiv-druginteractions.org or
http://hivclinic.ca/wp-content/uploads/2014/09/DDI-Tool_recreational-drugs_Eng.pdf

5.7. WHEN TO CONSIDER ALTERING TREATMENT

Primary sources of recommendation:
BHIVA Treatment Guidelines 2015-16
http://www.bhiva.org/HIV-1-treatment-guidelines.aspx

Indications for switching a component of an ART regimen include:

- Viral load repeatedly >50 copies/ml but previously <50 copies/ml even if <24 weeks therapy (2 tests at least 2 weeks apart). A repeat viral load should be performed to establish if this is a transient elevation or "blip". The decision to alter on the basis of viral load depends on several factors & should be discussed with a consultant. It depends on previous regimens, future options, adherence issues, clinical state & patient opinion.
- Steadily rising viral load (2 tests at least 2 weeks apart to confirm genuine rebound rather than a transient increase).
- Steadily falling CD4 count over 6 months (at least 2 tests).
- Clinical progression to AIDS/development or new complication of HIV disease.
- Regime simplification to improve adherence

IMPORTANT NOTES

- An early pharmacy referral should be considered so any adherence/absorption/interaction issues can be identified. This can often prevent the need to switch treatment.
- The antiretroviral advice team meet every week.
- If changing therapy with significant viraemia, take blood for resistance testing
- The new regimen should contain at least 3 active drugs including one from a new drug class. Active is defined as 'where a drug is likely to have significant antiviral activity in vivo based on the antiretroviral treatment history and the results of all current and previous genotypic resistance testing'.
- Remember that enzyme induction may persist for some time after cessation of the active drug

5.7.1 Switching therapy

Source: London Antiretroviral Therapy (ART) Prescribing Implementation Toolkit April 2017 NHS England

- For patients where a switch from a ritonavir-boosted PI to a Cobicistat-containing PI FDC is being considered, the need for long term PI use should be reviewed as cheaper, better tolerated drugs may be clinically appropriate.
- If a patient's regimen is being changed, consider switch of Truvada to abacavir/lamivudine where clinically appropriate (for cost reasons).
- Where cost-effective, clinically appropriate switches can be made, these should be actively considered for all stable patients in line with national and regional initiatives.

5.8. ARV ADVICE MEETING

The purpose of the Antiretroviral Discussion Group or ARV MDT is:

- to provide a forum for the peer review, team discussion and audit of antiretroviral prescribing decisions. The aim is to promote safe, rational, effective, and economic use of anti-retrovirals in line with NHSE commissioning policies and local procurement processes.

To ensure the purpose is met, the group is responsible for the following:

1. Providing expert clinical advice and guidance on the use of anti-retroviral medication based on evidence, policies and guidelines.
2. To aid prescribing decisions for initiation, switches for failure or resistance, and use of new agents are subject to peer review.
3. Patients needing to initiate or switch to a non-preferred regimen will be discussed in this meeting (see 5.4.1 *London ARV Algorithm for first line therapy*).
4. Promote and facilitate the education of all staff in anti-retroviral usage and resistance.

When non-preferred, or single-tablet, regimens are being considered for any reason (e.g. patient lifestyle, intolerance, toxicity, or viral resistance), these must be referred to the ARV Discussion Group before prescribing. Retrospective discussion is allowed where there is an immediate need to start or switch (e.g. PI/r and resistance).

Referral should use the ARV Advice Form and submitted by fax or email. Clinicians are strongly encouraged to present the case at the meeting themselves, or nominate a deputy.

The ARV Advice Team consists of:

- All HIV Physicians
- Specialist HIV/ID Pharmacists
- Specialist HIV Nurse
- Virologists
- Access to clinical psychology, community nursing, and social care

A minimum of 3 members with expert skills need to attend to ensure a face-to-face meeting is quorate. This must include the following specific members:

- HIV Physicians (2 minimum, and at least 1 Consultant)
- HIV/ID pharmacist (1 minimum, and at least one Band 8)

Available members will meet once weekly at St George's Hospital, Courtyard Clinic Seminar Room and discuss all submitted requests. The meeting has a nominated Chair (A named HIV Consultant). Deputisation for running the meeting will be to either a nominated deputy HIV Consultant or Specialist Pharmacist.

Reporting Procedures

- Virtual Clinic list of patient to discuss is booked on Millcare
- Outcome is documented in the notes and on Millcare under patient therapy
- Attendees will be recorded on Millcare
- Audit forms will be completed for starter and switch patients recording the reasoning for using non-preferred regimens using the LSCG audit proforma.

5.9. ADVICE TO PATIENT

- Do not stop taking the medication without first discussing it with your doctor.

- Taking these drugs intermittently will cause the virus to become resistant to current therapy and may limit the success of future drug combinations. Make sure that you always have a supply of medication. Do not let supplies run out.

- These drugs are not a cure for HIV. They have not been proven to prevent HIV transmission to other people through sexual contact or blood. Therefore appropriate precautions should continue to be used.

- Lack of data means that combination antiretroviral therapy cannot be guaranteed to be safe in pregnancy or prevent HIV transmission to the unborn child. Therefore, adequate contraception should be used. In women of childbearing potential, discussion about use of these drugs in pregnancy should be documented in the notes.

- See also advice which is specific to the administration of individual agents (section 5.3).

- See also advice on Adherence published by HIV Coordination Group. Any specific adherence issues can be discussed with the McEntee/Courtyard pharmacist.

5.10 HIV DOCUMENTATION

HIV Follow up clinic- each clinic letter to contain

Name
DOB
Sex
Year of diagnosis
Nadir CD4 count, Current CD4 count, Viral load; Any ART resistance mutations?
ART prescribed, adherence and tolerance
OI diagnoses, prophylaxis and screening (e.g. retinal screening for CMV)
Significant diagnoses
Complete drug history incl over the counter medications/ supplements
GP aware? Patient wants copy of letter?

All Patients- at least yearly

BP/ UPCR
Cholesterol/ lipid profile Smoking history
Assessment of cardiovascular health if > 40 (annual QRISK2 score)
Assessment of mental health
Assessment of bone health if >50years, post-menopausal women or others at high risk (FRAX score every 3 years)
Recommend flu vaccine and check pneumococcal vaccine received
Sexual history and offer sexual health tests (including STS) +/- condoms / contraception

Hepatitis

Check hepatitis A immune- if not vaccinate
Check hepatitis C status – if previous HCV infection screen with HCV RNA
Check hepatitis B status- if non- immune vaccinate (40 μg (double dose) strength of HBV vaccine should be used in HIV-infected patients and given at months 0, 1, 2 and 6) and check responses if anti-HBs <10 IU/L should be offered three further 40 μg doses of vaccine, given at monthly intervals, anti-HBs response >10 but <100 IU/L should be offered one additional 40 μg dose of vaccine

Screening for anti-HBs should be guided by the anti-HBs level measured after vaccination: every year for levels between 10 IU/L and 100 IU/L and every 2 years for higher levels.

Co-infection hepatitis B and HIV yearly viral loads (hepatitis B) and USS and aFP- consider co-infection clinic.
If Hep B have we looked for delta virus?

Women

Annual cervical smears
Plans for conception
Contraception discussion
Check if any children require HIV testing

MSM

Offer/recommend at least annual sexual health screening depending on risk
Consider Chemsex risk and refer to drug services if required
Consider anal smears for high risk patients
At least annual screening for STS, Hep C (RNA if previous infection) and Hep B sab/sag

6. TREATMENT OF HIV RELATED OPPORTUNISTIC & FUNGAL INFECTIONS

Primary sources of recommendation:

For treatment:
Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (2015)
https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

BHIVA Guidelines:
HIV Medicine 2011, 12 (Supp 2)
http://onlinelibrary.wiley.com/doi/10.1111/hiv.2011.12.issue-s2/issuetoc
http://www.bhiva.org/documents/Guidelines/OI/hiv_v12_is2_Iss2Press_Text.pdf

The Sanford Guide to HIV/AIDS therapy

BNF

6.1. PNEUMOCYSTIS CARINII (JIROVECI) PNEUMONIA

6.1.1. Pneumocystis carinii (jiroveci) Pneumonia Treatment

	DRUG	REGIMEN	ROUTE	COMMENTS
First line	Co-trimoxazole	120mg/kg/day in 2-4 divided doses **for 3 days**, (typically 8 or 9 x 960mg tablets/day) *then reduce to:* 90mg/kg/day in 2-4 divided doses **for a further 18 days** (total 21 days)	IV / PO	Reduce dose in renal impairment Dose should be based on actual body weight (for high doses, FBC and renal function should be monitored closely and dose reduce if necessary)
With adjunctive therapy	Prednisolone OR	40mg bd for 5 days, then 40mg od for 5 days, then 20mg od for the remainder of course	PO	**Use steroids for all patients with moderate / severe PCP** defined as hypoxaemia ratio < 0.5 $\frac{Pa\ O_2\ (kPa)}{\%\ inspired\ O_2} < 0.5$
	Methylprednisolone	30mg bd for 5 days, then 30mg od for 5 days, then 15mg od for the remainder of the course	IV	Start asap, probably 15-30min before or at the same time as other prescription or within 72h if not given initially

	DRUG	REGIMEN	ROUTE	COMMENTS
Second line	Clindamycin *WITH* Primaquine	> 60kg: 600mg qds 450mg qds < 60kg: 450mg qds 300mg qds for 21 days 15mg-30mg od for 21 days	IV PO IV PO PO	If IV clindamycin necessary infuse in 100ml 0.9% sodium chloride over 20-30 minutes Test for G6PD deficiency before administering primaquine Avoid primaquine in pregnancy and nursing mothers
Alternative second line	Trimethoprim *WITH* Dapsone	20mg/kg/day in 2-4 divided doses for 21 days 100mg od for 21 days	PO PO	Reduce dose of trimethoprim in renal impairment
Third line	Pentamidine	4mg/kg od for 21 days	IV	Reserved for severe cases only due to multiple toxicities
Alternative third line	Atovaquone suspension	750mg bd for 21 days	PO	Must be taken with food, particularly high fat meals For mild/moderate cases intolerant of 1st and 2nd line agents

6.1.2. Pneumocystis carinii (jiroveci) Pneumonia Prophylaxis

	DRUG	REGIMEN	COMMENTS
First line	Co-trimoxazole	960mg PO 3 times weekly (eg Mon, Wed, Fri) *Alternatives:* 480mg or 960mg od Daily therapy may be more effective but has lower tolerability	Prophylaxis is recommended for all patients with CDC Group IV disease or a CD4 count below 200/mm^3 In primary prophylaxis, co-trimoxazole can be stopped when the CD4 is > 100 for 3 months with an undetectable viral load[1] In secondary prophylaxis co-trimoxazole can be stopped when the CD4 is > 200 for 3 months with undetectable VL
Second line Monthly	Pentamidine	300mg inhaled once a month	• Pre-treat with salbutamol neb 2.5mg
Alternative second line Daily	Dapsone	100mg PO daily	
Alternative second line Weekly	Dapsone, *WITH* Pyrimethamine *WITH* Folinic acid	200mg PO weekly 75mg PO weekly 30mg PO weekly	

Another alternative = Atovaquone 1500mg od, taken with food. N.B. very expensive.

[1] COHERE study CID 2010, 51:611. http://cid.oxfordjournals.org/content/51/5/611.full.pdf+html

6.2. MYCOBACTERIUM AVIUM INTRACELLULARE COMPLEX (MAI or MAC)

TREATMENT	DRUG	REGIMEN	MONITOR	COMMENTS
First Line	Rifabutin ***PLUS*** Clarithromycin *OR* Azithromycin ***PLUS*** Ethambutol	300mg od PO 500mg bd PO 500mg od PO 15mg/kg od PO	U+E, LFT	Rifabutin: Reduce dose if CrCl <30ml/min Enzyme inducer. If on RTV-boosted PI: 150mg 3x weekly If on efavirenz: 450mg od. Warn patients to report uveitis (eye pain, redness, photophobia, blurred vision) Reduce dose if CrCl <30ml/min Baseline ophthalmic examination
Alternative First Line	Clarithromycin or azithromycin +ethambutol +rifabutin ***PLUS*** *one or more of* Ciprofloxacin *or* Levofloxacin *or* Moxifloxacin *or*	As above 500-750mg bd PO 500mg od PO 400mg od PO		 Ref CDC and John Hopkins
	Amikacin	10-15mg/kg IV/daily		See Section 8.3.6 for notes / cautions etc

<u>Caution: significant drug interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors</u>

Criteria for Discontinuing Chronic Maintenance Therapy (CDC/IDSA):
Completed ≥12 months therapy, ***and*** no signs/ symptoms of MAC disease, ***and*** sustained (>6 months) CD4+ count >100 cells/mm^3 in response to ART

6.3. CYTOMEGALOVIRUS INFECTIONS

6.3.1. CMV Acute/Induction Treatment

	DRUG	REGIMEN	ADMINISTRATION INSTRUCTIONS	MONITORING	COMMENTS
First line	Valganciclovir	900mg bd for 3 weeks	450mg oral tablet, with or after food	*For Valganciclovir or Ganciclovir:* FBC: twice weekly NB neutrophils + platelets	*For Valganciclovir or Ganciclovir:* • Reduce dose in renal impairment, i.e. Cr >125 • Care with AZT • Extreme caution if neuts <1.0 consider GCSF • 2% only get deranged LFT's • Monitoring as for Valganciclovir
Parenteral alternative	Ganciclovir	5mg/kg bd for 3 weeks	IV infusion in 100ml 0.9% Saline over 1 hour		
Second Line	Foscarnet	90 mg/kg bd for 3 weeks	IV infusion over 1-2 hours Peripheral line: dilute with equal volume of 5% dextrose via Y connector	Baseline Creat, Ca^{2+}, PO_4: then twice weekly, ensure good hydration	• Maintain fluid intake/output of 4-5L (total) in 24 hours • If nausea & vomiting occur, divide total daily dose into 3 equal infusions • Reduce dose in renal impairment i.e. Cr>100, not recommended if Cr>250 • 1 bottle = 500ml = 12g • Beware of hypocalcaemia • Care of genital ulceration – wash well after urination

6.3.2. Cytomegalovirus Infections: Maintenance Regimens for CMV Retinitis

	DRUG	REGIMEN	ADMINISTRATION INSTRUCTIONS	MONITORING	NOTES
First Line Oral	Valganciclovir	900mg od	with or after food		
First Line Parenteral	Ganciclovir	6mg/kg od on 5 days each week *OR* 5 mg/kg od on 7 days each week	IV infusion in 100ml 0.9% saline over 1 hour	As above	• Consider iv maintenance therapy if evidence of progression/relapse despite maintenance • Repeat induction regimen unless ganciclovir contraindicated or combination Rx with foscarnet • Resistance can develop
Second Line	Foscarnet	90-120mg/kg od on 5 to 7 days each week	IV infusion over 1-2 hours (Dilute as above if peripheral)	As above	• BHIVA recommends 90mg/kg od • If evidence of progression/relapse despite maintenance, repeat induction regimen unless foscarnet contraindicated • Cidofovir a 3rd line option, beware toxicity

Maintenance treatment can be stopped if there is good immune reconstitution (CD4 >100 cells/µl and undetectable viral load). This decision should be made following careful discussion between the HIV physician and the ophthalmologist involved in the patient's care.

6.4. TOXOPLASMOSIS

6.4.1. Toxoplasmosis Acute/Induction Treatment

Note - Induction treatment is usually given for at least 6 weeks

	DRUG	REGIMEN	ADMINISTRATION INSTRUCTIONS	MONITORING	COMMENTS
First Line	Sulphadiazine *PLUS* Pyrimethamine *PLUS* Folinic Acid	100mg/kg/day (1.5-2g qds) PO 200mg loading dose then 50mg od if <60kg, 75mg od if > 60kg 15mg od PO		FBC, LFTs Creat FBC	Avoid in severe renal impairment No IV formulation Crystalluria may occur. Reduce risk by high fluid intake. Treat by alkalinisation of urine.
Adjunctive Therapy	Dexamethasone	Initially 4mg qds PO/IV			If significant oedema or mass effect
	Consider Anti-convulsants				
Second Line	Clindamycin* *PLUS* Pyrimethamine *PLUS* Folinic Acid	600mg qds PO/IV))) As above	If IV necessary, infuse in 100ml 0.9% saline over 20-30 mins	LFTs, FBC	Absorption good so rarely need to use IV NB Cl difficile diarrhoea

* Alternatives to clindamycin include azithromycin 1-1.25g od, atovaquone (expensive), or clarithromycin

6.4.2. Toxoplasmosis Maintenance Regimens

	DRUG	REGIMEN	COMMENTS
First line *Prevents PCP and toxoplasmosis*	Sulphadiazine *PLUS* Pyrimethamine *PLUS* Folinic Acid	0.5g qds PO 25mg od PO 15mg od PO	Previous guidelines have recommended 0.5-1g sulphadiazine and 25-50mg pyrimethamine
Second line *Prevents toxoplasmosis only*	Clindamycin *PLUS* Pyrimethamine *PLUS* Folinic Acid	300mg qds PO 25mg od PO 15mg od PO	Alternative 450mg tds Pyrimethamine dose – as above
Possible alternatives	Pyrimethamine *PLUS* Atovaquone *PLUS* Folinic Acid *Or consider* Azithromycin	25-50mg od PO 750bd-qds PO 15mg od PO 1-1.25g od PO	

Maintenance regimens may be discontinued if sustained rise in CD4 count >200 for >3 months. BHIVA suggests CD4>100 may be safe.

6.5. OROPHARYNGEAL and OESOPHAGEAL CANDIDIASIS

	DRUG	REGIMEN	ROUTE	COMMENTS
First line	Fluconazole	100-200 mg od 7-14 days	PO	Dose 200-400mg/d PO/IV if oesophageal candidiasis
Fluconazole-resistant or intermediate Candida sp (C glabrata, C krusei) OR Poor clinical response NB. Usually responds well to effective ART	Caspofungin[1]	70 mg IV loading dose followed by 50mg IV od for 7 days, if no response continue for another 7 days	IV	Daily dose=70mg if weight>80kg

1. voriconazole is another option, but interactions with antiretrovirals may be significant and data are limited (contraindicated with Efavirenz)

IDSA updated References:

1. Pappas PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Clin Infect Dis. 2016 Feb 15;62(4):e1-50.
2. Perfect JR, et al. Clinical practice guidelines for the management of cryptococcal disease: Clin Infect Dis. 2010 Feb 1;50(3):291-322.
3. Patterson TF, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016. Clin Infect Dis. 2016 Aug 15;63(4):e1-e60

6.6 ANTIFUNGAL THERAPY: SYSTEMIC CANDIDIASIS & ASPERGILLOSIS

NB – Amphotericin must be prescribed by BRAND NAME; AmBisome® and Fungizone® are not interchangable

CONDITION	TREATMENT DRUG	CHOICE OF DRUG	COMMENTS
Candidaemia and invasive candidiasis	**Caspofungin** 70 mg IV od day 1, 50 mg IV od thereafter *or* **Fluconazole** 400mg bd (day 1, total dose 12mg/kg), then, 400-800mg/day (6mg/kg) (PO/IV) *plus* **Remove existing central lines**	Factors favouring initial caspofungin: - patient unstable - prior azole therapy, - unknown *Candida* species Factors favouring initial fluconazole – - patient stable - no prior azoles - known C. albicans, C.parapsilosis,or C.tropicalis	Switch to oral fluconazole if possible from speciation/susceptibility If fluconazole resistance, use caspofungin or voriconazole Treatment duration: 2 weeks after last positive blood culture and resolution of symptoms and signs. Extend if organ involvement
Invasive Aspergillosis	**Voriconazole** 6 mg/kg bd IV day 1 then 4 mg/kg bd thereafter Oral dose (>40kg): 400 mg bd day 1 (if not previously loaded), 200mg bd thereafter *second line:* **AmBisome®** **(Liposomal Amphotericin)** 3 mg/kg/day *Salvage:* **Caspofungin** *70mg IV od on day 1, followed by 50mg IV od thereafter (70mg/day maintenance dose if wt >80kg)*	Watch for drug interactions Monitor liver function, 20% oriental patients are poor metabolisers – check levels Given dose and duration required, conventional AmB is best avoided Data only in salvage treatment for caspofungin	Treatment duration 6-12 weeks Switch to oral Voriconazole as soon as possible (oral bioavailablility 96%) Avoid IV formulation if creatinine clearance <50 ml/min due to accumulation of IV vehicle. Take at least one hour before or after food. Halve maintenance dose in mild/moderate hepatic cirrhosis Consider adjuvant surgery if focal disease or lesions impinging great vessels or major airways Combinations of voriconazole + anidulafungin showed trend towards improved outcome in a clinical trial (Marr KA et al. Ann Intern Med. 2015 Jan 20;162(2):81-9) Consider in selected patients - **seek senior advice**

6.7. CRYPTOCOCCAL MENINGITIS

Usual treatment: 2 weeks induction with Amphotericin plus flucytosine followed by 8 weeks high-dose fluconazole

DRUG	REGIMEN	ADMINISTRATION INSTRUCTIONS	MONITOR	COMMENTS
AmBisome® (Liposomal Amphotericin)	*3-4 mg/kg/day, od*		Cr, U&Es LFTs, Mg FBC	Monitor K / Mg **at least every other day** - renal loss common Replace as required (refer to grey book for oral/ iv formulation)
PLUS				
Flucytosine	100mg/kg/day IV/PO for 14 days	In 4 divided doses - infuse each dose over 20-40 min Tabs available, but unlicensed	Cr, FBC	Consider dose reduction in renal impairment. Dose-related leukopenia and thrombocytopenia, especially in renal failure / concurrent use of other marrow suppressants.
FOLLOWED BY: Fluconazole	400mg bd ONE DAY, then od, **8 weeks**			Reduce dose in renal impairment. Increase dose by 50% if on concomitant rifampicin
MAINTENANCE Fluconazole	200mg od PO			Reduce dose in renal impairment Consider discontinuing if CD4>100 /ul with VL suppression for ≥3months Initiate ART 4-10 weeks from start of antifungal treatment

** Reactions to amphotericin such as fever, rigors, abdo pain, muscle pain, nausea & vomiting are common. Reactions may be reduced by pretreatment with **paracetamol/hydrocortisone IV/ chlorpheniramine IV** which should be given if such reactions occur, but not routinely.*

Management of raised intracranial pressure in Cryptococcal meningitis
Elevated CSF opening pressure (>20cm) is common. Always measure when doing LP. Consider serial LP if pressure >25cm H2O.
Serial LP: Remove 10ml CSF, recheck pressure; if pressure still >20cm, remove further 10ml and recheck- up to maximum volume removal of 30ml. Repeat LP next day unless marked clinical improvement.

7. TREATMENT OF BACTERIAL INFECTIONS

Primary source of recommendation:
Local Guidelines: Antimicrobial prescribing policy and Trust guidelines
http://stginet/Units%20and%20Departments/Antimicrobial%20prescribing%20information/Antimicrobial%20Prescribing%20Info%20for%20staff.aspx
Microguide desktop version: http://microguide.horizonsp.co.uk/viewer/sguh/adult or download from app store
Also see "Guidelines for the Management of Common Medical Emergencies and For the Use of Antimicrobial Drugs":
http://stginet/Publications/Clinical%20Publications/The%20Grey%20Book.aspx

National / International Guidelines:
BIS guidelines:
https://www.britishinfection.org/guidelines-resources/published-guidelines/

TUBERCULOSIS: BNF Reference 5.1.9
NICE guidelines: https://www.nice.org.uk/guidance/ng33/
CDC guidelines: https://www.cdc.gov/tb/publications/guidelines/default.htm
WHO guidelines: http://www.who.int/publications/guidelines/tuberculosis/en/

7.1 PNEUMONIA IN ADULTS

Follow local guidelines as above – CAP treatment recommendations currently:

	1st-line Antibiotics	Alternative / 2nd-line	Oral Switch	Duration
NON SEVERE (CURB-65 score 0-1)	Doxycycline PO 200mg STAT then 100mg OD	Amoxicillin PO 500mg - 1g 8hrly		5-7 days
SEVERE (CURB-65 score 2-5)	Benzyl Penicillin IV 1.2g 4hrly *PLUS* Doxycycline PO 200mg STAT then 100mg OD (or Clarithromycin IV 500mg 12hrly if unable to take oral)	Levofloxacin IV/PO 500mg OD	Amoxicillin 500mg-1g 8hrly ± Doxycycline PO 200mg STAT then 100-200mg OD Or continue levofloxacin if started	7-10 days in total IV+PO (Review need for doxycycline on oral switch)

If clinical suspicion of PVL-SA pneumonia, see PHE guidelines:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/322857/Guidance_on_the_diagnosis_and_management_of_PVL_associated_SA_infections_in_England_2_Ed.pdf

7.2. BACTERIAL MENINGITIS

Primary source of recommendation:
Local Guidelines: http://microguide.horizonsp.co.uk/viewer/sguh/adult
National / International Guidelines:
Meningitis: BNF Reference 5.1
http://www.journalofinfection.com/article/S0163-4453(16)00024-4/fulltext
Meningococcal disease: https://www.britishinfection.org/files/5414/5674/3289/algorithm.pdf

7.2.1. Use of CT prior to LP in suspected meningitis

- Never delay appropriate antibiotic therapy whilst awaiting CT scan.
- Treat suspected meningococcal disease (i.e. typical rash) immediately (after blood cultures are drawn) with intravenous Ceftriaxone ± Aciclovir ± Amoxicillin
- In meningococcal septicaemia, LP may be irrelevant, as management is not affected by presence/absence of meningeal involvement. The priority is prevention of shock syndrome.
- A normal CT does not rule out possible herniation due to increased intracerebral pressure
- Look for clinical signs suggestive of intracranial hypertension, even with normal CT
- Consider risk-benefits carefully before performing LP – Discuss with on-call consultant.
- Monitor carefully for signs of impending herniation.

ALWAYS PERFORM a CT of the head before LP in patients with one or more clinical features that increase the likelihood of having intracranial mass lesions / increased CSF pressure:

- immunosuppression / HIV (risk of toxoplasma encephalitis or CNS lymphoma)
- dilated or poorly reactive pupils or ocular palsies
- papilloedema
- hemiparesis
- tonic / focal seizures
- rapid or major decrease in the level of consciousness
- bradycardia (also consider typhoid in differential diagnosis)
- irregular respirations
- decerebrate or decorticate posture
- GCS ≤12
- Focal neurological signs

ALWAYS DISCUSS CT FINDINGS WITH CONSULTANT/ SpR before proceeding to LP.

If none of the above are present:
* Draw blood for culture
* Take throat swabs for bacteriology
* Start empirical antibiotics according to clinical situation
* Discuss with SpR / consultant whether CT to be requested and LP performed.
Outside working hours it may be possible to delay CT/LP until the next morning.

Remember need for paired serum glucose with LP.

If CT is not performed - Continue to observe for signs of raised intracranial pressure. If seen, perform CT AT ONCE and consider LP, but only after discussion with SpR/Consultant.

7.2.2 Antibiotic treatment

DRUG	REGIMEN	ADMINISTRATION INSTRUCTIONS	MONITOR	COMMENTS
Ceftriaxone OR *if sensitive*: Benzylpenicillin [1]	4g OD IV 2.4g IV every 4h	Infuse over 60 minutes Infuse over 60 min in 100ml of 0.9% NaCl or 5% dextrose	FBC U+E, Creat	If *H. influenzae* or penicillin resistant pneumococci suspected Duration: N. menigitidis – 5 days S penumoniae – 10-14 days H. influenza – 10 days
ALTERNATIVE TREATMENT Take senior advice				
Chloramphenicol	2g qds IV/PO (25mg/kg QDS)	Slow IV bolus over at least 5 minutes	FBC, LFTs, Creat	If *H. influenzae* suspected
If Listeria suspected: Amoxicillin	 2g 4 hourly IV 120mg tds IV	 Slow IV bolus Slow IV bolus or infuse over 30mins in 50ml 0.9% sodium chloride	U+E, Creat	If Listeria confirmed treat for 21 days
Immunocompromised Ceftriaxone + Amoxicillin	 4g OD IV 2g 4 hourly IV	 Slow IV bolus Slow IV bolus	FBC U+E, Creat	*Includes diabetics and history of alcohol misuse.* *Also consider if >55yrs old*

[1] In patients treated with penicillin alone for meningococcal meningitis give ciprofloxacin to eliminate nasopharyngeal carriage and in meningitis caused by *Haemophilus influenzae* give rifampicin to eliminate pharyngeal carriage at the end of treatment.
For prophylaxis of contacts of meningococcal cases, current HPA guidelines recommend a single dose of ciprofloxacin.

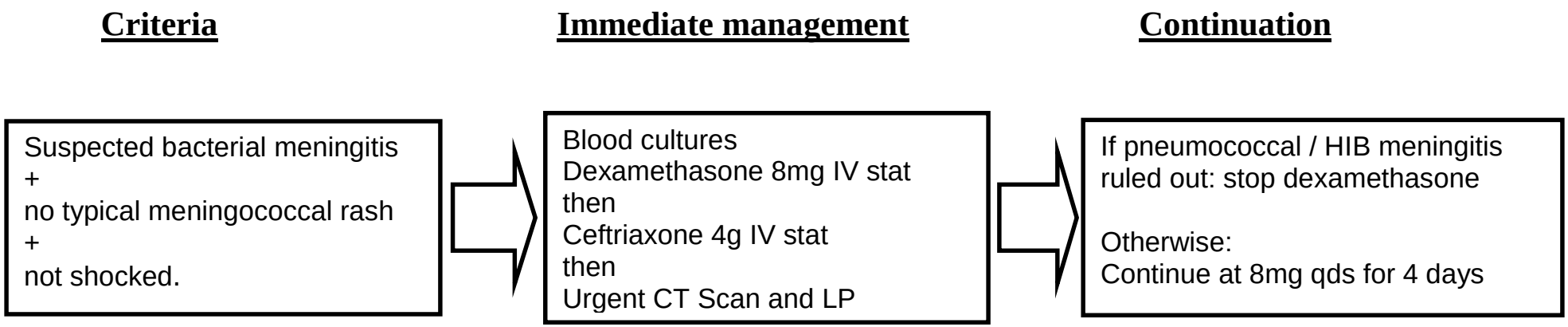
CONSIDER ADDITION OF ACICLOVIR IF VIRAL ENCEPHALITIS SUSPECTED – See section 9.1.1

CONSIDER ADDING IV Vancomycin or IV/PO rifampicin if the patient has been to a country where penicillin resistant pneumococci are prevalent in the last 6 months. http://www.journalofinfection.com/article/S0163-4453(16)00024-4/fulltext

Contact the Consultant in Communicable Disease Control at the local PHE Health Protection Unit at the time of clinical diagnosis (via air-call through hospital switchboard)

7.2.3. Steroids in Meningitis

Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2010 (9):CD004405. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004405.pub3/abstract



These guidelines are largely based on the findings of the De Gans study, according to which those patients most likely to benefit from steroids are those with pneumococcal meningitis with decreased GCS at presentation. *See*. http://www.nejm.org/doi/pdf/10.1056/NEJMoa021334

- In the study, steroids were given before or with antibiotics; there is no clinical evidence for, but insufficient data to exclude, a benefit of steroids given after antibiotics.
- Given the likely safety of dexamethasone and the prolonged nature of the pro-inflammatory CSF response in pneumococcal meningitis, if a patient has received pre-admission antibiotics, dexamethasone should still be given as soon as possible according to the above criteria. BIA guidance advises giving up to 12 hours after initial antibiotic dose
- Encouragement for GPs to give Benzylpenicillin prior to admission in patients with suspected bacterial meningitis should continue.

The Dutch experience (Bijlsma et al Lancet ID 2015) suggests that steroids may be advantageous in all groups: http://www.ncbi.nlm.nih.gov/pubmed/26652862

7.2.4. Protection/Prophylaxis: Invasive Meningococcus/ H. Influenzae B

See HPA guidance (links below) and https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

!! - Contact the CCDC at the time of clinical diagnosis (air-call through hospital switchboard.) CCDC may recommend chemoprophylaxis in patients who fall outside of the criteria below.
Protection: UK guidelines recommend wearing face masks and eye protection when there is a risk of secretions splashing into face and eyes.

Who should receive prophylaxis:

NEISSERIA MENINGITIDIS MENINGITIS & SEPTICAEMIA http://www.journalofinfection.com/article/S0163-4453(16)00024-4/fulltext#sec7	HAEMOPHILUS INFLUENZAE B (HIB) ALL CASES OF INVASIVE DISEASE https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/231009/Revised_recommendations_for_the_preventions_of_secondary_Haemophilus_influenzae_type_b_disease.pdf
CASE Chemoprophylaxis is not necessary if the disease has already been treated with ceftriaxone Penicillin does not eliminate carriage therefore give chemoprophylaxis to the case when able to take oral medication and before discharged from hospital. CONTACTS Offer chemoprophylaxis to ***close contacts*** of cases, irrespective of vaccination status; CCDC normally arranges this. Contacts should also be vaccinated with polysaccharide vaccine. Notify GP to arrange vaccination of the case and appropriate contacts.	CASE Give chemoprophylaxis if age <10 years old or if vulnerable individuals in the household. If index case was previously immunised against HIB, notify British Paediatric Surveillance Unit as a vaccine failure. Paediatric cases: Discuss with Paediatric ID Unimmunised cases up to age 10 should be immunised as recurrence of HIB can occur. Immunised cases up to age 10 should have convalescent antibody levels checked CONTACTS If there is an **at risk** individual in the household, then **the case** and **ALL** household contacts should receive chemoprophylaxis, regardless of immunisation status At risk individuals include: ♦ Children under 4 ♦ Vulnerable people (eg immunosuppressed or asplenic) of any age All unimmunised household contacts under the age of 10 should be immunised

N.B. Warn contacts / families that late disease may occur despite prophylaxis.

Chemoprophylaxis for meningitis

	Meningococcus
Adults and children >12yrs	Ciprofloxacin 500 mg stat
Children: 5 – 12 yrs	Ciprofloxacin 250 mg stat
Children: 1 mo – 4yrs	Ciprofloxacin 125 mg stat
Alternative	Rifampicin
Adult	600mg bd for 2 days
1-12 years	10mg/kg bd (up to max 600mg bd) for 2 days
1-12 months	5mg/kg bd for 2 days

	Haemophilus Influenzae Type B
Adult	Rifampicin 600mg od for 4 days
Child (3 months to 12 yrs)	Rifampicin 20mg/kg (max 600mg) od 4 days
Infant (1-3 months)	Rifampicin 10mg/kg od for 4 days

The use of single dose **ciprofloxacin** is recommended by a Cochrane review and current PHE guidelines for prophylaxis of contacts of **meningococcal disease**,

Single dose ciprofloxacin: Risk of Anaphylaxis: Give information sheet that includes the risk of side effects, and be prepared to deal with allergic reactions.

Rifampicin Syrup contains 100mg in 5ml. Do not use in known severe liver disease. Warn about discoloration of urine, saliva and tears (soft contact lenses). Consider drug interactions, eg oral contraception rendered ineffective, therefore use additional barrier method for remainder of that cycle.

<u>Further cases</u>
If further cases of meningococcal disease occur within a group of close contacts <4 weeks after receiving rifampicin prophylaxis, use ciproflaxacin (or ceftriaxone) for repeat prophylaxis.

7.3. INFECTIVE ENDOCARDITIS

Primary source of recommendation:
Local Guidelines: http://microguide.horizonsp.co.uk/viewer/sguh/adult
National / International Guidelines:
ESC guidelines https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Infective-Endocarditis-Guidelines-on-Prevention-Diagnosis-and-Treatment-of
IDSA guidelines http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/IDSA_Practice_Guidelines/Fever_and_Infections/AHA%20Infective%20Endo.pdf

Suspected Endocarditis: take blood cultures (several sets, plus a serum sample), request an ECHO & seek an urgent review by a senior cardiologist. The decisions as to when to start treatment depends on the severity of illness – in general terms, clinical sepsis should not go untreated.

If an organism is identified – Discuss with Microbiology Consultant and see specific guidelines on Microguide

If the organism is unknown, and there are no clinical indicators as to likely pathogen - consider empiric therapy as below.

All endocarditis patients are discussed in the cardiology/infection MDT every Wednesday morning 9-10. Patients should be discussed with microbiology or cardiology consultant first.

REMEMBER TO TAKE BLOOD CULTURES BEFORE GIVING ANTIBIOTICS

Empirical Therapy - Likely/proven endocarditis. See full guidelines on Microguide for pathogen directed therapy

Clinical situation	Other criteria	Antibiotics	Comment
Empirical therapy	Native valve or late prosthetic valve (>1 year post surgery)	Amoxicillin 2g 4hrly + Flucloxacillin 2g IV 4 hrly + Gentamicin 3 mg/kg OD	Adjust Gent so that Trough (ie pre-dose) < 1 and Peak (1h post dose) 10 - 12 mg/l
		Pen allergy: Vancomycin IV as per Trust guidelines + Gentamicin 3mg/kg OD	Adjust Gent so that Trough (ie pre-dose) < 1 and Peak (1h post dose) 10 - 12 mg/l Adjust Vanc so that trough levels = 15-20 mg/L
	Early prosthetic valve (<1 year post surgery)	Vancomycin IV as per Trust guidelines + Rifampicin 600mg 12hrly PO + Gentamicin 3mg/kg OD	Adjust Gent so that Trough (ie pre-dose) < 1 and Peak (1h post dose) 10 - 12 mg/l Adjust Vanc so that trough levels = 15-20 mg/L

Notes: All antibiotics to be given IV unless otherwise specified.

Vancomycin: Trough levels of 15-20mg/l should be maintained - higher than the usual level recommended with this antibiotic. Vancomycin generally preferred to teicoplanin, as there is more experience with this drug, levels can be performed in-house, and treatment failures with Staphylococci treated with Teicoplanin have been reported.

Antibiotic treatment of Fungal, Vancomycin Resistant Enterococcal and Prosthetic Valve endocarditis of any cause is likely to fail and surgery is very frequently required.

8. TUBERCULOSIS

8.1 TOP TIPS FOR TB PATIENTS

CLINIC LETTER/ DISCHARGE SUMMARIES

List clearly at the top the diagnosis and any other important co- morbidities

State clearly on what basis the diagnosis was made- i.e. sputum smear positive, culture confirmed, pulmonary/extrapulmonary, or presumed TB with all tests negative to date.

List important outstanding results including any drug sensitivities awaited/ follow-up scan. List important negatives i.e. smear negative/ CXR clear
N.B. if GeneXpert positive with no detection of resistance mutations for Rifampicin this suggests but does not prove full sensitivity- there may still be INH resistance or rare Rif resistance.

List treatment history- start date/ drugs used/ step down date or planned step down date/ planned duration of therapy/ any breaks in treatment/ if unusual regime, the reason(s) for it/ supervision- full DOT/ weekly nurse led review/ unsupervised.

List all other medication taken - remember the multitude of interactions particularly with Rifampicin.

Body of the text: A few brief lines on how they are getting on.

Plan of action: List clearly- tests performed in clinic/ amount of medication prescribed/ when you are next seeing them.

Copies: Do not forget to copy to TB nurses, other physicians involved, and patient if they wish.

IN CLINIC
Turn up early and check in with receptionist - look through your list to see if any difficult patients or tests to chase
Check you know diagnosis basis/ treatment history etc, as above
Check through the results
Check HIV test done, and Hep B&C also appropriate in most patients
Check Vit D level done, and supplements/IM injection given as per Trust guidelines
Assess patient

Go through drugs with them- make sure they know to bring ALL drugs that they are on:
Are the doses they are taking correct? Are the doses that they are swallowing the same as in the notes?
Any interactions? Esp. OCP in women - remind them and document
Renal impairment - ethambutol doses need adjustment / liver impairment - the rest!
Any side effects/adverse reactions? Document both positives and negatives
Eyes with ethambutol (if on long term ethambutol can provide regular Ishihara and Snellen tests in clinic)
Peripheral neuropathy
Nausea/ vomiting/ inability to take
Check urine is red and document.

Investigations-
In pulmonary TB - CXR minimum at 2/12 and end of treatment.
Spines - unless there is any neurology, re-image at the end of treatment only.
Try not to irradiate young people too often- remember the changes take a long time to resolve.
LFTs - initially monthly then can go longer if all well.
Continue getting sputa until smear- and culture- negative.

Time to step down?
Are sensitivities back? If not, wait….
If pulmonary TB check CXR, sputum smear- and culture-negative
Adherence issues? check with nurses
Any breaks in therapy?
Take all old medicines away and explain the new tablets - remind them of the importance of adherence

Time to stop?
Check adherence - check in with TB nurses
Any gaps in treatment?
Check type of TB
NB duration extended to one year for CNS/ miliary TB.
Treatment may be prolonged if the disease is very disseminated/ taking a long time to become smear- and culture negative/ there is spinal involvement/ inability to take all standard medication.
Radiology at end - full/partial resolution?
Any outstanding results/ anything for the GP to re-check - ?anaemia, vit D, etc.
No need to follow patients off treatment UNLESS there were particular issues, but make sure you tell the patient and write in your letter that you are happy to see at short notice should symptoms reoccur.

Contacts assessed?

Document the quantity of treatment prescribed - max a month of treatment unless very exceptional circumstances.

At end of consultation check the patient knows if tests needed/ nursing review needed/ when doctor will see them next- at the minimum monthly nursing review, if all stable can leave it several months before doctor review

Would an interpreter help next time? Ask for one!

AT END OF CLINIC

Meet with consultant and TB nurse to talk through patients.
Keep a copy of the clinic list.
Remember to chase results afterwards, and add to the end of your letter.
Keep a copy of the letters sent by Wanda in file on trust computer in case of lost letters/ things to check.

8.2. STANDARD UNSUPERVISED 6 MONTH REGIMEN – INDIVIDUAL DRUGS

See: BNF, section 5.1.9; Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control
The National Collaborating Centre for Chronic Conditions: https://www.nice.org.uk/guidance/ng33

DRUG	REGIMEN	DURATION (Months)	ADMINISTRATION INSTRUCTIONS	MONITORING	COMMENTS
Rifampicin *PLUS*	≤50kg : 450mg od PO ≥50kg : 600mg od PO	6	30mins-1 hour before food (breakfast usually)	LFTs	Potent enzyme inducer Warn if on oral contraceptive pill Warn re discolouration of urine
Isoniazid *PLUS*	300mg od PO	6	30mins-1 hour before food	LFTs	
Pyrazinamide *PLUS*	≤50kg : 1.5g od PO ≥50kg : 2g od PO	2		LFTs	Induction only Unlicensed medicine
Ethambutol	15mg/kg od PO	2			Induction only Full ophthalmic examination prior to treatment

- Include pyridoxine 10mg PO od and consider higher dose (up to 100mg PO od) in patients receiving isoniazid with malnutrition / factors predisposing to pyridoxine deficiency. Routine use of pyridoxine is justifiable.
- Modify treatment regimen according to drug susceptibility testing once this becomes available.
- Duration of treatment: Normally 2/12 induction plus 4/12 maintenance. Increase in CNS disease to 12 months total, or if therapy is interrupted.
- Add glucocorticoids in pericardial or CNS disease.
- If spinal bone disease appears to involve meninges, treat as CNS disease (add steroids / extend to 12 months).
- Treatment may need to be modified in patients also receiving antiretroviral therapy because of interactions.
- Look for vitamin D deficiency and replace as appropriate according to Trust guidance.

8.3. PARENTERAL REGIMENS

DRUG	REGIMEN	ADMINISTRATION INSTRUCTIONS	COMMENTS
Rifampicin	600mg od	IV infusion in 500ml dextrose 5% over 2-3hr. If fluid restricted, may be given in 100ml over 30mins	Liaise with Pharmacy re supply
Isoniazid	300mg od	Slow IV bolus	

8.4. COMBINATION REGIMENS FOR UNSUPERVISED, ORAL THERAPY

PATIENT WEIGHT (kg)				
INDUCTION	< 40	40-49	50-64	≥ 65
Rifater *PLUS*	3 od	4 od	5 od	6 od
Ethambutol (15mg/kg, to nearest 100mg)	≤ 600mg od	600-800mg od	800-1000mg od	≥1000mg od
CONTINUATION				
	Rifinah 150/100: 3 tablets od		*Rifinah 300/150*: 2 tablets od	

8.5. COMBINATION DOSE REGIMENS: DIRECTLY OBSERVED THERAPY (DOT)

Use a daily dosing schedule to patients with active TB, and consider 3 x weekly dosing only if a risk assessment identifies a need for DOT and enhanced case management; and daily DOT is not possible.

These doses are given 3 times a week under supervision

PATIENT'S WEIGHT (kg)					
	40-50	50-60	60-65	65-70	70-80
DRUG					
Rifampicin	600mg	900mg	900mg	900mg	900mg
Isoniazid *	600-800mg	800-900mg	900-1000mg	1000-1100mg	1100-1200mg
Pyrazinamide	2g	2.5g	2.5g	2.5g	2.5g
Ethambutol (30mg/kg)	1.2-1.6g	1.6-1.8g	1.8-2.0g	2.0-2.2g	2.2-2.4g

* Some authorities (WHO, BNF, CDC) cap dose at 900mg maximum; BTS guidelines do not - they recommend 15mg/kg 3 times a week.
See: http://www.tbdrugmonographs.co.uk/rifampicin.html.

8.6. TREATMENT OF TUBERCULOUS MENINGITIS

Primary source of recommendation: National / International Guidelines: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=13422
Key References: Thwaites et al (NEJM 2004, 351:1741-51): http://content.nejm.org/cgi/reprint/351/17/1741.pdf;
Ruslami et al 2013: http://www.ncbi.nlm.nih.gov/pubmed/23103177

DRUG	DOSE REGIMEN	COMMENTS
Rifamipicin, Pyrazinamide And Ethambutol/Moxifloxacin[Δ] PLUS Isoniazid PLUS	Rifampicin: 900mg (or 15mg/kg) for 2 months, followed by 600mg if <70kg, 900mg if ≥70kg Moxifloxacin 400mg OD. Pyrazinamide and Ethambutol dosing as above. 5mg/kg od	Use daily dosing Extend total treatment duration to 12 months Consider IV administration if any concerns about effectiveness of oral therapy. Moxifloxacin dose may be increased to 800mg OD. Ethambutol may be withheld if eye toxicity cannot be monitored Some authorities have suggested using 10mg/kg/day (ref: Humphries M. The management of tuberculous meningitis. Thorax. 1992;47(8):577-81)
Prednisolone*	20–40 mg if on rifampicin, otherwise 10–20 mg	Withdraw gradually, starting within 2–3 weeks of initiation, according to signs/symptoms and progress

[Δ] Moxifloxacin is favoured over ethambutol for CNS penetration and to avoid eye toxicity.
* Prednisolone is recommended in the RCP guidelines. The pivotal study used **dexamethasone** at the following doses (note mg/kg/d versus mg/day):

Week:	1	2	3	4	5	6	7	8
Disease Severity	Dexamethasone dose							
Grade I (GCS 15, no focal neurology)	**Intravenous – mg/kg/day**		Oral mg/kg/day		Oral – total mg/day			
	0.3	0.2	0.1	3	2	1	-	-
Grade II/III (GCS<15 or focal neurology)	**Intravenous – mg/kg/day**				Oral – total mg/day			
	0.4	0.3	0.2	0.1	4	3	2	1

8.7 TREATMENT FOR PERICARDIAL TUBERCULOSIS

Primary source of recommendation:
Key References:
Mayosi BM *et al*. Interventions for treating tuberculous pericarditis. Cochrane Database of Systematic Reviews 2002, issue 4. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000526
Strang JIG *et al*. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. QJM 2004; 97 (8): 525-535. http://qjmed.oxfordjournals.org/content/97/8/525.long

The standard 6-month regimen of anti-tuberculous treatment (see above sections 8.2 to 8.5) with the addition of steroids is still advised in the NICE guidance for all patients but has recently been changed to only high risk patients (large pericardial effusions, early signs of constriction) in the American Thoracic Society guidelines 2016.

Steroid regimen:

NICE guidelines recommend starting with prednisolone 60mg/day and gradual withdrawal after 2 to 3 weeks of initiating treatment.
The main studies in this topic used the following protocol:

	Weeks 1-4	Weeks 5-8	Weeks 9-10	Week 11	Week 12
Prednisolone	60mg od	30mg od	15mg od	5mg od	Stop

8.8. TREATMENT OF MDR TUBERCULOSIS

Guidance: WHO Guidelines for the programmatic management of drug-resistant tuberculosis:
http://www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/
http://www.who.int/tb/areas-of-work/drug-resistant-tb/MDRTBguidelines2016.pdf

- Treatment of MDR-TB is highly specialized and must be discussed with the CIU Consultant.
- All patients should be started on WHO standard duration regimens and not the short course 'Bangladesh' regimens.
- Intensive phase should include at least four second-line anti-tuberculosis drugs likely to be effective based on DST, whole genome sequencing results or epidemiological links plus pyrazinamide.
- Intensive phase should be ≥6 months (or ≥4 months after culture conversion) with total treatment duration ≥18 months after culture conversion (assuming no previous treatment for MDR-TB). The WHO 2011 and 2016 guidelines recommend a longer duration of treatment – intensive phase for ≥8 months and total treatment duration ≥20 months, though this approach is debatable at present.

Microbiology

- Consider MDR-TB in all cases – rates highest in Eastern Europe / Central Asia and cases who have received TB treatment previously, particularly where there was poor adherence.
- Check PCR is being done for all new smear positive sputa (should be done routinely)
    - PCR may be performed on non-respiratory samples – but discuss first
- Ensure an isolate, or primary sample, has been sent to the MTB Reference Laboratory for full susceptibility testing. Samples can be fast-tracked if results are needed urgently – the Micro department can arrange this on request.
- Treat Rifampicin-resistance (e.g. RpoB mutation detected by GeneXpert) as MDR until proven otherwise
    - (Rif mono-resistance does occur but is uncommon)
- Send multiple "baseline" cultures pre-treatment
- If the initial sample is not sputum, send ≥3 sputum samples (induced if necessary) and take CXR -important for infection control / discharge planning
- Request HIV test (with consent) – as for all TB patients

General Management

- Ensure CIU Consultant and TB nurses are aware
- Admit to S/R 2 or 3 on McEntee ward – Isolate as below
- Notify Public Health (if not aware)

Baseline Safety / Monitoring

- Baseline bloods: FBC, U&E, LFT, Glucose, CRP
- Baseline Audiology (injectable agents) Baseline Ophthalmology (ethambutol/linezolid toxicity)

Choice of Regimen at SGH

STEP 1 Add fluroquinolone- moxifloxicin (unless on bedaquiline, delamanid)
STEP 2 Add injectable agent- capreomycin (unless resistant)
STEP 3 Add 2 'likely active' of: prothionamide, cycloserine, PAS, linezolid > clofazimine
STEP 4 Add ethambutol and pyrazinamde if sensitive
STEP 5 consider WHO D1-3 drugs if unable to make up a four drug (plus Z) regimen: Bedaquiline, Delamanid, high dose INH, meropenem-clavulanate

NB this scheme does not follow the 2016 guideline groups precisely but is used at SGH
For example: Cm, Mfx, Pto, Cs/Lzd plus E Z

- Check doses / documentation (for unlicensed drugs) with Pharmacist.

Monitoring during treatment

- Efficacy / infection risk: For pulmonary disease repeat sputum microbiology weekly to discharge then fortnightly (induced if necessary)
- Toxicity:
    - Bloods twice weekly initially – see specific toxicities
    - ECG weekly if on moxifloxacin, bedaquiline, or delamanid.
    - Audiology if symptomatic or at least monthly if on amikacin or other risk factors
    - Opthalmology – (check baseline) - repeat if visual symptoms and on E or Lzd

Discharge / Follow-up

- See Table below; follow-up Prof Harrison Wed AM clinic
- OPAT if appropriate

Liaise closely with TB nurses (x1466)

8.8.1. Drugs used for MDR TB

WHO Group	Drug	Dosage	Administration	Adverse effects	Comments	Monitoring
A	**Moxifloxacin (Mfx)**	400mg OD PO 600mg OD PO has been used for suspected FQ resistance MDR-TB short course regimen *(safety of the higher doses not verified) – WHO* *Weight <30kg: 400mg OD* *Weight 30-50kg: 600mg OD* *Weight >50Kg: 800mg OD*	400mg tablets	Occasional: GI intolerance, headache, malaise, insomnia, restlessness, dizziness, allergic reactions, diarrhoea, photosensitivity, prolonged QT, tendonitis	600mg dose unlicensed Do not give with calcium containing therapy (eg Adcal): reduced absorption	Baseline and weekly ECGs for QTc **G6PD deficiency:** Risk of haemolytic reactions when treated with quinolones.
	Levofloxacin (Lfx)	1g OD PO	500mg tablets	As above	Use instead of Mfx when on bedaquiline or delamanid due to long QT concerns	As above

WHO Group	Drug	Dosage	Administration	Adverse effects	Comments	Monitoring
B	**Capreomycin**	15-20mg/kg (max 1g) OD IM or IV Can reduce to 3x/wk during continuation phase	IM: 1g vial + 2ml N/S or WFI* IV infusion: as above then further dilute in 100 ml N/S or 5%D* Infuse: 30-60 min	Frequent: nephrotoxicity, tubular dysfunction, proteinuria, urticaria, rash Occasional: ototoxicity, electrolyte abnormalities: (↓ K, Mg) Injection site pain/ abscess	IV infusion unlicensed but allowed in information from manufacturer Consider increasing dosing interval if balance problems	Similar for all injectables: Baseline: (all patients) • U+E • Audiometry Follow-up: U+E at least monthly, more if high risk (age, DM, HIV, renal disease) Audiometry if symptomatic or monthly if high risk <u>TDM:</u> post-induction and if toxicity
	Amikacin	15-20mg/kg (max 1g) OD IM or IV Can reduce to 2-3x /wk during continuation phase.	IM: undiluted IV: dilute to 2.5mg/ml (N/S or 5%D*) Infuse over 30 min	Frequent: nephrotoxicity (proteinuria, electrolyte abnormalities: ↓K, Mg) pain at injection site Occasional: Ototoxicity vestibular toxicity, peripheral neuropathy, rash, eosinophilia	Penicillins: in vitro antagonism Manufacturer suggests max cumulative dose of 15g (not mentioned in WHO guidelines)	<u>TDM</u>: twice weekly
	Streptomycin	15-20mg/kg (max 1g) OD IM only Can reduce to 2 -3x/wk after initial period	IM: 1g vial + 2ml WFI*	Nephrotoxicity, electrolyte abnormalities (↓ K, Mg, Ca), ototoxicity, vestibular toxicity, local pain at injection site	Recommended max cumulative dose 100g	<u>TDM:</u> post-induction and if toxicity

* N/S = normal saline, WFI = water for injections, 5%D = 5% dextrose

WHO Group	Drug	Dosage	Administration	Adverse effects	Comments	Monitoring
C	**Prothionamide**	15-20mg/kg/day (max 1g) PO To improve tolerance increase dose gradually over a few days	250mg and 500mg tablets Should be taken with or after meals to reduce gastrointestinal adverse effects	Frequent: GI intolerance Occasional: allergic reactions, depression, drowsiness, dizziness, restlessness, headache, neurotoxicity, optic neuritis, hepatitis, postural hypotension, hypothyroidism (↑risk with PAS)	Unlicensed – complete forms All patients must be prescribed pyridoxine whilst receiving prothionamide. The usual adult dose ranges from 50 to 100mg daily, up to 50mg per 250mg of Prothionamide.	FBC, U+E, LFTs, glucose TFTs: baseline then ≥ 6-monthly Ophthalmology r/v at baseline and periodically during therapy
	Cycloserine	10-15mg/kg/day (max 1g) PO To improve tolerance increase dose gradually over a few days	250mg capsules Best taken on an empty stomach	Frequent: neurological and psychiatric disturbances Occasional: visual changes, rash, numbness, paraesthesia, jaundice Rare: Suicidal thoughts, seizures	Contraindicated in epilepsy, depression, psychosis, alcohol dependence. All patients must be prescribed pyridoxine whilst receiving cycloserine: 50-100 mg daily, up to 50mg per 250mg of cycloserine	TDM to ensure adequate plasma levels and identify toxicity
	Para aminosalicylic acid (PAS) (now a WHO group D3 agent but based on cohort data so placed here at SGH)	150mg/kg/day or 8-12g PO in 2-3 divided doses To improve tolerance increase dose gradually over a few days	4g sachets (granules) Take with food to reduce gastrointestinal adverse effects.	Frequent: GI intolerance, anorexia, diarrhoea, hypothyroidism (↑ risk with prothionamide) Occasional: hepatitis, allergic reaction, thyroid enlargement, malabsorption syndrome, ↑INR, fever	Unlicensed – complete forms Do not use if patient allergic to aspirin. Store refrigerated Suspend in orange /apple juice or sprinkle over yoghurt	FBC, U+E, LFTs, clotting TFTs: baseline then ≥ 6-monthly

	Linezolid	600mg od PO/IV Dose reduce to 300mg od if side effects or stop	600mg tablets	Frequent: diarrhoea, nausea, vomiting, headache Occasional: bone marrow suppression, anaemia > thrombocytopenia, optic neuropathy, peripheral neuropathy	Side effects more frequent on long term therapy (> 28 days) Avoid large amounts of tyramine containing foods (mature cheese, yeast extracts, undistilled alcoholic beverages, fermented soya bean products) Interactions with some antidepressants	Baseline: • FBC • Ophthalmology r/v Follow-up • FBC weekly Warn patients: report visual symptoms immediately (blurred vision, visual field defect, colour vision) → urgent ophthalmology r/v And if any changes in sensation on feet.
	Clofazimine	100-300mg OD PO Consider starting at 300mg OD and reducing to 100mg after 4-6 weeks	50mg and 100mg capsules Clofazimine should be taken with meals or with milk to maximise absorption and reduce GI side-effects	Frequent: ichthyosis, pink to brownish-black discoloration of skin, cornea, retina and urine, anorexia and abdominal pain	Unlicensed – complete forms May reduce absorption of rifampicin Modest reduction of bioavailability if ingested with orange juice	Consider acute abdomen secondary to crystal deposits if abdominal pain occurs

WHO Group	Drug	Dosage	Administration	Adverse effects	Comments	Monitoring
D1	**Pyrazinamide**	< 50 kg: 1.5g OD PO > 50 kg: 2g OD PO	500mg tablets	Hepatotoxicity, GI upset, arthralgia, anaemia, thrombocytopenia, rash		LFTs
	Ethambutol	15-30mg/kg OD PO	100mg (yellow) 400mg (grey) tablets	Optic neuritis		Baseline Ophthalmology Monitor visual acuity if symptomatic
D2	**Bedaquiline**	Week 1-2: 400mg OD Week 3-24: 200mg 3x/wk **PLEASE COMPLETE BLUETEQ FORM PRIOR TO PRESCRIBING**	100mg tablets. Bedaquiline should be taken with food. Use for a maximum of 24 weeks. Half-life: ~ 5.5 months	Frequent: nausea, arthralgia, headache. Occasional: QT interval prolongation, hepatic.	Do not use if QT interval >500ms; Hx of torsades de pointes or ventricular arrhythmias; or severe coronary artery disease. Caution in hepatic/renal impairment. Avoid co-administration of strong CYP3A4 inducers; cautious use of CYP3A4 inhibitors. Do not give with delamanid	Monitor QT interval. U&Es, calcium, magnesium, LFTs
	Delamanid **PLEASE COMPLETE BLUETEQ FORM PRIOR TO PRESCRIBING**	100mg BD for 24 wks.	50mg tablets Delamanid should be taken with food.	Frequent: nausea, vomiting, dizziness. Occasional: anxiety, paraesthesia, tremor. Patients must be consented and must sign consent as increased deaths in the active trial arm	Do not use if QT interval >500ms; Hx of torsades de pointes or ventricular arrhythmias; or severe coronary artery disease. Do not use if serum albumin <2.8g.dL. Do not give with bedaquiline.	Monitor QT interval. U&Es, calcium, magnesium, serum albumin level.

D3	**Meropenem & Co-amoxiclav**	Meropenem 1g TDS IV Co-amoxiclav 325mg TDS PO	1g vial by injection or IV infusion: diluted in 500ml 5%D or N/S* Infuse over 30 mins 325 mg tablets (250/125)	Frequent: nausea, vomiting, diarrhoea, rash, pruritus Occasional: cholestatic jaundice, prolonged bleeding time, thrombocytopenia, eosinophilia, Stevens-Johnson syndrome	Do not give if penicillin allergic Cholestatic jaundice more common if > 65 years, male, long term treatment	FBC, LFTs
	Amoxicillin & Co-amoxiclav	Amoxicillin 500mg TDS PO Co-amoxiclav 625mg TDS PO	500mg tablets 625mg tablets (500/125)	As above	Do not give if penicillin allergic	FBC, LFTs

8.9. ISOLATION AND DISCHARGE OF PATIENTS WITH TB

Primary source of recommendation:
The Interdepartmental Working Group on Tuberculosis. The Prevention and Control of Tuberculosis in the United Kingdom. September 1998
http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4006196&chk=y9pK72
BTS Guidelines: Control and prevention of tuberculosis in the United Kingdom: Code of Practice 2000. Thorax 2000; 55:887-901.
http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/TB.pdf
TUBERCULOSIS, Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE guidance 2011.
http://www.nice.org.uk/guidance/index.jsp?action=byID&o=13422
Local Guidelines
Infection Control Policy 2007; Appendix D, Clinical Care Protocol 26
Protocol for the Care of Patients with Tuberculosis
http://stginet/Policies/Patient%20related/Infection_Control/Clin_2_0_AppD_Prot26.pdf
National / International Guidelines:
Listed at:
http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733847842?p=1191942150143

- Manage all patients with suspected or confirmed pulmonary TB as potentially infectious.
- This does not necessarily mean admission: BTS recommend that "treatment … should be undertaken in the patient's home whenever possible".
- Test all smear positive patients for *RpoB* gene mutations – if positive, admit and treat as MDR-TB until cultures confirm sensitivities.
- Patients with smear-positive drug-sensitive TB usually become "non-infectious" after two weeks of treatment including rifampicin and isoniazid.
- Patients admitted with proven or suspected pulmonary TB should remain in respiratory isolation for at least two weeks of appropriate treatment.
- If patients with proven or suspected pulmonary TB remain inpatients for longer than two weeks, or are readmitted AT ANY STAGE in their illness, even if on effective treatment, they remain in a side-room – do NOT nurse on the open ward. **Continue respiratory isolation throughout their admission.** This means they should remain in their rooms or wear a mask if they leave. *This exceeds generic BTS guidelines but is appropriate because of the enhanced risk of infection for immunosuppressed individuals being managed in the same environment.*
- BTS guidelines recommend that patients being moved to a setting (inpatient or home) with HIV-infected or immunocompromised individuals should **additionally** have a minimum of 3 negative sputa over at least 14 days, and tolerate and adhere to treatment and show clinical response in terms of either fever or cough.

8.9.1. MDR TB Isolation and Discharge Planning

Policy was agreed with Infection Control and HPA Dec 2009

Evidence of Pulmonary disease	Sputum Smear†	Culture	Isolation	OPAT	Room	Masks
Yes	Pos	Pos	Isolate in SR until 3 cultures (over ≥2 wks) negative at 6 weeks culture i.e. minimum isolation ≥8 weeks	Not usually considered before 6 weeks culture negativity i.e. Can be home isolated from 6 weeks culture negativity	Rooms 2/3 if possible	FFP3
Yes	Neg	Pos	Isolate in SR if in-patient. Consider home-isolation if feasible	Offer at > 4 weeks culture negativity* if feasible	Rooms 2/3 if possible	FFP3
Yes	Neg	Neg @>6wk	Maintain in SR if in-patient	Plan for OPAT as soon as feasible	SR	Discuss
No	Neg	Neg §	Maintain in SR if in-patient	Plan for OPAT as soon as feasible	SR	None

† Induced sputum if necessary

* Requirements for OPAT: BUPA Occupational Health require ≥4 weeks treatment and ≥4 weeks culture negativity, plus non-coughing/ clinical response.

§ No need to wait for culture results if case can be defined as non-pulmonary?

Definitions

Side Room (SR) isolation – patients should only leave the room to attend investigations, in which case they should be wearing an FFP3 mask.

“Non-Infectious”: at least 3 samples, culture negative at 6 weeks, collected over a period of at least 14 days.

XDR TB – must be “non-infectious” before discharge

8.9.2. What sputum test to use for Diagnosis and Monitoring of TB

In the context of suspected Pulmonary TB:

Cough with sputum production	**For diagnosis**	**AFB smear**	**Persisting productive cough**	**For monitoring**
Yes	3 x Sputum	Positive	Yes	Weekly sputum while still productive cough, from second week of treatment onwards
			No	No monitoring once cough resolves or is non-productive
		Negative	Yes or No	Treat – no need to monitor sputum Low infectivity risk
No	3 x **Induced Sputum** or BAL		No	No further monitoring
			New sputum production	Reassess clinically and send sputum AFB and culture
Monitoring in Special Circumstances:				
HCW / Nursery Nurse / Other high risk of infection				Weekly **Induced Sputum** may be used to confirm non-infectivity / safe return to work
MDRTB – suspected or proven			Yes	Weekly sputum to ≥6 weeks, then monthly
			No	Weekly **Induced Sputum** to ≥6 weeks, then monthly

9. VIRAL INFECTIONS

Primary source of recommendation:
SPC, BNF Reference 5.3.2, The Sanford Guide to HIV/AIDS therapy; Micromedex Healthcare Series
Varicella Zoster Clinical management:
Reference: British Infection Society: Chickenpox in adults and Clinical management: Journal of Infection (2008) 57, 95e102

9.1. HERPES SIMPLEX

9.1.1. Herpes Simplex treatment

	DRUG	IMMUNE STATUS	ORAL REGIMEN	INTRAVENOUS REGIMEN	COMMENTS
First line	Aciclovir	Immune competent	200mg 5x daily or 400 mg 3 x daily 5 days	5mg/kg tds *	For oral aciclovir, ensure dose interval <6h. eg 6, 10, 14, 18, MN
		Immunosuppressed (HIV)	400mg 5x daily 5 days	5mg/kg tds *	Sanford suggests 400mg tds 7-10 days for all
Alternative	Valaciclovir	Immune competent Immunosuppressed (HIV)	500mg bd for 5-10 days 1g bd for 10 days		Sanford suggests 1g bd for 7-10 days for all
Second line (Aciclovir resistant)	Foscarnet	All		40mg/kg 8-hourly IV for 21 days	
H.simplex encephalitis	Aciclovir	All		10mg/kg tds, 10-21 days *	Page: 87 Sanford, CDC and John Hopkins suggest duration 14-21days, BNF states at least 10 days

* Aciclovir infusions are given over 1 hour at $\leq$ 5mg/ml (e.g. 500mg in 100ml). Dosed according to ideal body weight.
Maintain adequate hydration if using IV route. Monitor renal function - **Dose reduce aciclovir and valaciclovir in renal impairment**
Therapeutic drug monitoring is available. Please contact virology to discuss.

9.1.2. Herpes Simplex Suppression

	DRUG	IMMUNE STATUS	ORAL REGIMEN	INTRAVENOUS REGIMEN	COMMENTS
First line	Aciclovir	Immune competent Immunosuppressed (HIV)	400mg bd 200–400 mg 4x daily		
Alternative	Valaciclovir	Immune competent Immunosuppressed (HIV)	250mg bd or 500mg od 500mg bd		Or Famciclovir 250-500mg bd but note greater cost

In individuals with good immune function, mild infection of the eye and lips (herpes labialis) may be treated with a topical aciclovir. (BNF)

Aciclcovir resistance: If suspected, please contact virology to discuss arranging virological confirmation.

9.2. HERPES ZOSTER

	DRUG	IMMUNE STATUS	ORAL REGIMEN	INTRAVENOUS REGIMEN	COMMENTS
First line	Aciclovir	Immune competent Immunosuppressed	800mg : 5x daily 7 days 800mg : 5x daily for 7 days or 2 days after crusting of lesions	5mg/kg tds * 10mg/kg tds *	For oral aciclovir, ensure dose interval <6h. eg 6, 10, 14, 18, MN
Alternative	Valaciclovir		1g tds 7 days		

* Aciclovir infusions are given over 1 hour at ≤ 5mg/ml (e.g. 500mg in 100ml). Maintain adequate hydration if using IV route. Monitor renal function.
Dose reduce aciclovir and valaciclovir in renal impairment

9.2.1 Varicella Vaccination

- Varicella vaccination is recommended for non-immune healthy close contacts of immunocompromised patients.
- A clear history of chickenpox or shingles is considered to be adequate evidence of immunity in those brought up in temperate climes, although it can be less reliable in adults born and raised in areas of low seroprevalence.
- Lack of immunity should be confirmed by testing for VZV IgG in serum prior to immunisation as asymptomatic infection is common.
- VZIG may be offered up to 10 days after exposure, but is ideally administered within 7 days of contact with an infective case of chickenpox or exposed shingles.

9.3 INFLUENZA

Primary source of recommendation:
BNF section 6.5
NICE: Treatment: http://guidance.nice.org.uk/TA168 - Prophylaxis: http://guidance.nice.org.uk/TA158

Local Guidelines: http://stg1wordpress01/wordpress/wp-content/uploads/2016/06/Influenza-Protocol.pdf

National / International Guidelines (PHE) :
https://www.gov.uk/government/collections/seasonal-influenza-guidance-data-and-analysis
Jan 2016 guidelines: https://www.gov.uk/government/publications/influenza-treatment-and-prophylaxis-using-anti-viral-agents

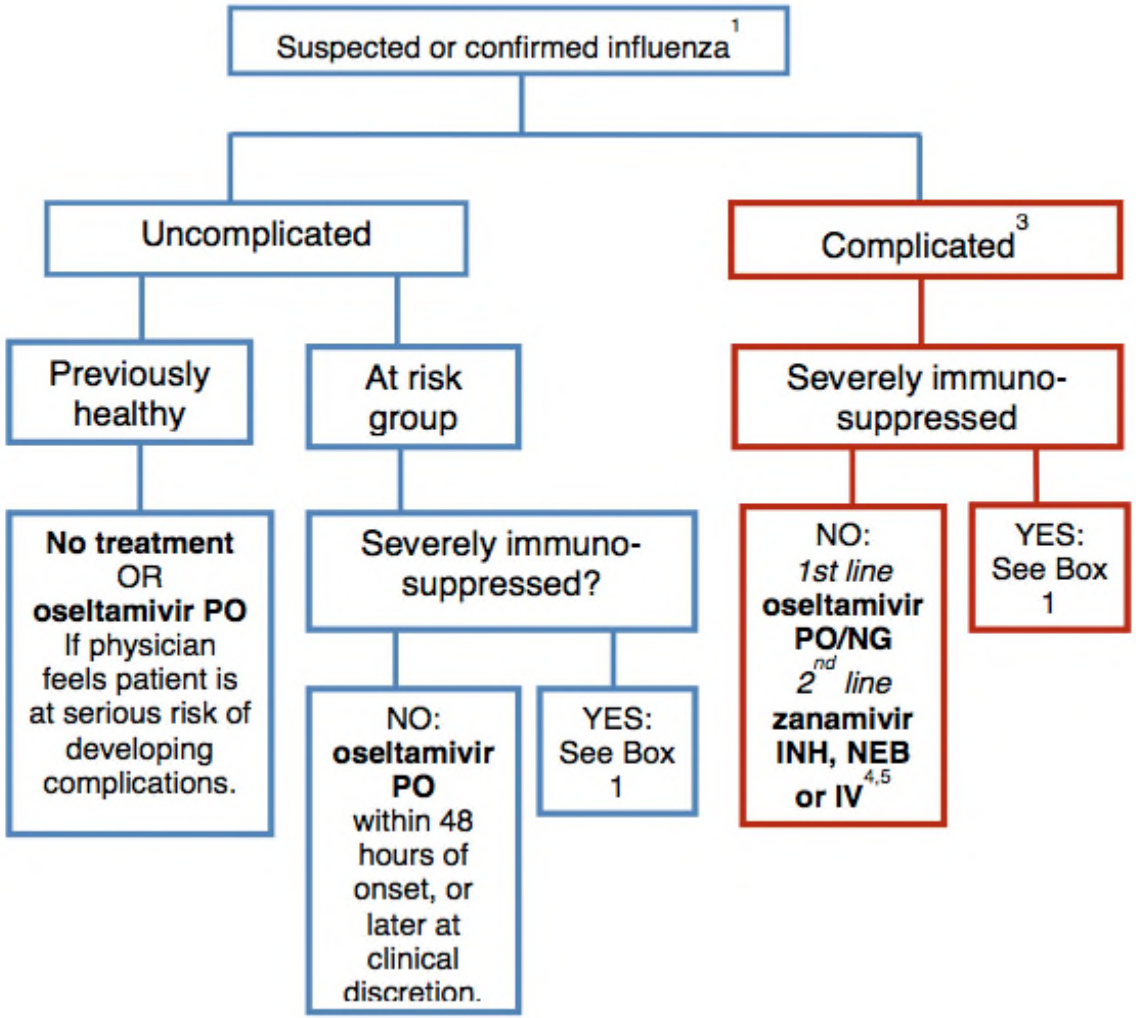
9.3.1 Treatment

NICE recommends the use of zanamivir or oseltamivir for flu-like illness in people at risk of developing complications when flu rates reach a threshold "circulating" level, provided treatment starts within 48 hours of symptoms.

"At risk" are:

- Age ≥65 years
- Neurological, hepatic, renal, pulmonary and chronic cardiac disease (does not include uncomplicated hypertension)
- Diabetes mellitus
- Chronic respiratory disease
- Immune-deficiency or suppression (for definitions see above PHE/NICE guideline)
- Morbid obesity (BMI >=40).
- Pregnancy (including up to two weeks post partum).
- Children under 6 months of age

Algorithm: Selection of antiviral therapy for treatment of influenza



Definitions for algorithm

1. **Uncomplicated influenza:** Influenza presenting with fever, coryza, generalised symptoms (headache, malaise, myalgia, arthralgia) and sometimes gastrointestinal symptoms, but without any features of complicated influenza.

2. **Complicated influenza:** Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition

Box 1: Selection of antivirals for severely immunosuppressed patients

Dominant circulating strain[2]	Uncomplicated influenza	Complicated influenza[3]
Lower risk of oseltamivir resistant strains eg A(H3N2)	**oseltamivir PO** and clinical follow up Within 48 hours of onset or later at clinical discretion	***1st line:*** **oseltamivir PO/NG** *2nd line:* zanamivir INH[4], NEB or IV[5] Consider switching to zanamivir if: - Poor clinical response - Subtype testing confirms A(H1N1)
Higher risk of oseltamivir resistant strains e.g A(H1N1)	**zanamivir INH (Diskhaler)** within 36 hours of onset or later at clinical discretion OR if unable to take inhaled preparation[4] **oseltamivir PO** and clinical follow up. Within 48 hours of onset or later at clinical discretion	**zanamivir INH, NEB or IV[5]** within 36 hours of onset or later at clinical discretion (if there are delays in obtaining aqueous zanamivir, use oseltamivir as a bridging treatment until zanamivir is available)

Treatment dosages

DRUG	REGIMEN	COMMENTS
Oseltamivir ("Tamiflu")	75mg bd PO for 5 days May increase to 150 mg (off label dosage) in critically ill patients	Tamiflu is pre-packed in adult treatment courses GI and CNS side-effects may occur; rarely hypersensitivity Cautions: renal impairment, pregnancy, breast-feeding IV oseltamivir is available as an alternative but there is very limited experience of its use in the UK.
Zanamivir ("Relenza")	10mg bd INH for 5 days	This is an inhaled preparation NB: Other inhaled preperations should be given first Rarely hypersensitivity reactions may occur, bronchospasm Cautions: asthma, chronic pulmonary disease, pregnancy Zanamivir solution for IV is available on a compassionate use basis – this is unlicensed Use IV zanamivir in patients who have already failed to respond to nebulised zanamivir; patients who have developed respiratory conditions affecting nebuliser delivery (e.g. airways disease, pulmonary oedema); patients who have multi-organ involvement or are on intensive care IV zanamivir is renally excreted - dose modify in renal dysfunction dialysis renal Use of zanamivir for up to 10 days if resistance to oseltamivir suspected is an unlicensed duration.

9.3.2 Prophylaxis

Prophylactic dosages

DRUG	REGIMEN	COMMENTS
Oseltamivir ("Tamiflu")	75mg od PO for at least 10 days	For up to 6 weeks during an epidemic. Side-effects and cautions as above.
Zanamivir ("Relenza")	**Adults and children >5 years: 10mg od** 10 days	

Prophylaxis Guidelines

	Exposed to circulating influenza H1N1 (2009), H3N2, or B	**Exposed to suspected or confirmed oseltamivir resistant influenza**
Previously healthy (excluding pregnant women)	No prophylaxis	No prophylaxis
At risk of complicated influenza (including pregnant women but excluding severely immunosuppressed patients and children under 5 years)	**Oseltamivir PO 10 days once daily** if therapy can be started within 48 hrs of last contact; or after 48 hrs on specialist advice only	**Zanamivir INH 10 days once daily** if therapy can be started within 36 hrs of last contact; or after 36 hrs on specialist advice only.
Severely immunosuppressed patients (excluding children under 5 years)	**Zanamivir INH 10 days** if therapy can be started within 36 hrs of last contact; or after 36 hrs on specialist advice only. If unable to administer zanamivir INH, **oseltamivir PO 10 days** (if therapy can be started within 48 hrs of last contact; or after 48 hours on specialist advice only).	**Zanamivir INH 10 days** only if therapy can be started within 36 hrs of last contact; or after 36 hrs on specialist advice only. If unable to administer zanamivir INH, discuss with specialist and consider nebulised aqueous zanamivir (unlicensed) after individual risk assessment.

NICE recommends oseltamivir for post-exposure prophylaxis in at-risk adults and adolescents/residents in care establishments

10. TRAVEL-ASSOCIATED DISEASE

Primary source of recommendation:
Incubation periods adapted from: Illness after International Travel. Ryan, ET, Wilson, ME, & Kain, KC. M.D. NEJM 2002, 347(7):505-516 http://content.nejm.org/cgi/reprint/347/7/505.pdf
which also contains information on geographic distribution and mode of transmission

Useful links to sites with reliable country-specific, up-to-date and practical information (eg at risk areas for specific infections, required immunisations, current outbreaks etc). They both have links to the specific disease/infective agent, useful for a quick reminder on transmission modes, incubation periods, treatment etc

- Search eg ´NathNac´: UK´s National Travel Health Network and Centre (NathNac): https://travelhealthpro.org.uk/
- Search, eg ´CDC travel´: CDC (U.S. government and Centers for Disease Control and Prevention): https://wwwnc.cdc.gov/travel.

Other:

- Search ´Green book PHE´ for UK´s PHE detailed guidance on **vaccine-preventable diseases** : https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book
- Search ´CDC parasites´for U.S.'s CDC specific **parasitology website**: https://www.cdc.gov/parasites/index.html including life cycles, clinical details, management etc. Good for a quick update when needed. Note that some diagnostic procedures/treatments may not apply to the UK practice
- **Eosinophilia in returning travellers**: UK recommendations, practical advice and suggested order of investigations based on symptoms, travel history etc. http://www.journalofinfection.com/article/S0163-4453(09)00360-0/pdf

National / International Guidelines:
Malaria: BNF Reference 5.4.1
UK Malaria treatment guidelines 2016:
http:/www.journalofinfection.com/article/S0163-4453(16)00047-5/pdf

General considerations: admit if unwell or necessary for diagnosis. If well, consider discharge and review in either rapid access clinic on Mcentee or the infectious diseases clinic on Tuesdays (outpatient´s department). In both cases, this needs to be discussed with the CIU Spr on call for a formal referral.

10.1 INCUBATION PERIODS

Disease	Incubation period Usual (range)
Incubation <14 days	
Undifferentiated fever	
Malaria (Plasmodium species)	6 days to years
Dengue (dengue virus serotypes 1, 2, 3 and 4)	4–8 days (3–14 days)
Spotted fever (Rickettsiae)	About 1 week (a few days to 2–3 wk)
Scrub typhus (*Orientia tsutsugamushi)*	10 days (6–21 days)
Leptospirosis (*Leptospira interrogans* serotypes)	7–12 days (2–26 days)
Campylobacteriosis, salmonellosis, shigellosis	2–6 days (1–20 days)
Typhoid fever (*Salmonella enterica*, serotype typhi)	7–18 days (3–60 days)
Acute human immunodeficiency virus infection	Acute illness, 10–28 days (10d –6 wk)
East African trypanosomiasis (*Trypanosoma bruce/ rhodesiense*)	Acute illness, 5–16 days (3–21 days); chronic illness, months to years
Fever with haemorrhage	
Meningococcaemia, leptospirosis and other bacterial infections	}
Malaria	}3–14 days (2 days to 2 months)
Viral haemorrhagic fever	} VHF generally <21d
Fever with involvement of the central nervous system	
Meningococcal meningitis, many viral and bacterial forms of meningitis and encephalitis, malaria, typhoid, and typhus	
Rabies	1–2 months (9 days to years)
Arboviral encephalitis	3–14 days (1–20 days)
Angiostrongyliasis, eosinophilic meningitis	2 weeks (5 days to 4–6 wk)
Poliomyelitis	7–14 days (3–35 days)
East African trypanosomiasis	as above
Fever with respiratory findings	
Influenza	1–3 days
Legionellosis (*Legionella pneumophila*)	5–6 days (2–10 days)
Acute histoplasmosis (*Histoplasma capsulatum*)	Acute illness, 7–14 days (3–21 days)
Acute coccidioidomycosis (*Coccidioides immitis*)	Acute illness, 10–14 days (7–28 days)
Q fever (*Coxiella burnetii*)	14–21 days (2–29 days)
SARS	2-10 days (WHO and PHE definition <10 days, but may be more)

Disease	Incubation period Usual (range)
Incubation 14 days to 6 Weeks	
Malaria	6 days to years
Typhoid fever	7–18 days (3–60 days)
Hepatitis A	28–30 days (15–50 days)
Hepatitis E	26–42 days (2–9 wk)
Acute schistosomiasis (*Katayama fever*)	Katayama fever, 4–8 weeks
Amoebic liver abscess (*Entamoeba histolytica*)	Weeks to months
Leptospirosis	*As above*
Acute human immunodeficiency virus infection	*As above*
East African trypanosomiasis	*As above*
Viral haemorrhagic fever	*As above*
Q fever	*As above*
Incubation >6 Weeks	
Malaria	*As above*
Tuberculosis	Primary, weeks; reactivation,years
Hepatitis B	60–90 days (45–180 days; rarely 9 mo)
Visceral leishmaniasis (*Leishmania donovani, L. chagasi, others*)	2–6 months (10 days to years)
Lymphatic filariasis (*Wuchereria bancrofti* and other filariae)	3–6 months or longer
Schistosomiasis	*As above*
Amoebic liver abscess	Weeks to months
Chronic mycosis	1 week to years
Hepatitis E	*As above*
Rabies	*As above*
African trypanosomiasis (*T. brucei rhodesiense, T. brucei gambiense*)	Chronic illness, months to years

10.2. TREATMENT OF MALARIA

Primary source of recommendation:
BNF section 5.4.1; Sanford Guide
Local Guidelines:
National / International Guidelines: UK malaria treatment guidelines:
http://www.journalofinfection.com/article/S0163-4453(16)00047-5/fulltext

10.2.1 Non falciparum Malaria or Chloroquine resistance unlikely

DRUG	REGIMEN	COMMENTS
Chloroquine base (oral)	600mg base stat, then 300mg base after 6-8 hours, then 300mg base od for 2 days Example: Avloclor® tablets: 4 stat 2 6-8 hours later,then 2 od for 2 days	One chloroquine tablet (Avloclor®) is 250mg and contains 155mg of base. Chloroquine alone is adequate for *P.malariae* infections. Check G6PD status then follow with: • 15mg primaquine od for 14 days if P.ovale. • 30mg primaquine od for 14 days if P.vivax Avoid primaquine in pregnancy and nursing mothers N.B. If concerned about resistant vivax malaria (i.e failure of chloroquine-persistent symptoms or parasites) treat using artemether/lumefantrine or malarone as below.

N.B. The positive identification of non-faciparum malaria eg vivax seen on film, does not exclude falciparum co-infection.
Always treat severe malaria or high parasitaemia as falciparum.

10.2.2 Uncomplicated falciparum malaria or species unknown

Uncomplicated, able to take oral treatment

First choice: *Riamet 20/120* Artemether/lumefantrine	Six doses of 4 tablets at: Baseline, 8, 24, 36, 48 and 60 h	Anorexia, headache, cough and nausea/vomiting are common side-effects Do not use in first trimester of pregnancy. Be aware of QT effects. Follow on with Doxycycline/Clindamycin is not necessary.
Or *Malarone* Atovaquone/proguanil	4 tabs od PO 3 days	
Alternatives: Quinine sulphate	600mg tds PO 5-7days	Followed by Doxycycline/ Clindamycin as below In pregnancy use quinine rather than malarone, followed by clindamycin
Quinine treatment should be followed / accompanied by:		
Doxycycline, OR Clindamycin	200mg od PO 7 days 450mg tds PO 7 days	May be commenced at any time during quinine treatment or sequentially after the quinine course Clindamycin is an alternative, particularly in pregnancy.

Parasitaemia>2% or unable to tolerate oral treatment or pregnant women following specialist advice

First choice; Artesunate *	2.4 mg/kg IV at 0, 12 and 24 hrs, then daily thereafter	Supplied as 60mg vial. Add the 1ml sodium bicarbonate 5% diluent into the artesunate vial and shake for 2-3 mins. Then add 5ml of glucose 5% or sodium chloride 0.9% (to give a 10mg/ml solution) Inject the required amount of drug at a rate of 3-4 ml/min (i.e slow IV bolus) Give a full course of PO Riamet (first choice) or Malarone when the patient can tolerate oral therapy. Delayed haemolysis can occur 7-21 days post treat in 10-15% patients; check Hb 14 days post treatment completion.
Alternative if first choice not available; *Intravenous* Quinine dihydrochloride	Loading dose 20mg/kg (max 1.4g) then after 8-12 h, 10mg/kg tds IV (max 700mg) Infuse over 4 hours in 250-500ml of 5% dextrose until patient can swallow. Availability may be an issue	**<u>IMPORTANT</u> - The loading dose of 20mg/kg should NOT be used if the patient has received mefloquine, quinine, quinidine or halofantrine during the previous 24 hours.** Take baseline ECG; check for prolonged QTc (>0.44s or >25% increase form baseline) or other abnormality. Monitor ECG during therapy. Patients on IV quinine should receive IV 5% dextrose infusion 8 hourly to prevent hypoglycaemia. Blood glucose MUST be monitored 4 hourly (2 hourly during the infusion) OR if the condition deteriorates. If parenteral treatment given for > 48h and renal / multi-organ failure: reduce dose to 10mg/kg bd Change to an oral agent as soon as possible; ese as for uncomplicated falciparum malaria (a complete course should be given once IV therapy stopped). If oral quinine used - complete a 5-7 day course of quinine **Follow-on treatment with Doxycycline or Clindamycin if quinine used required as above.**

General notes: Careful fluid management is critical – fluid overload may occur
*Artesunate is supplied as a water soluble intravenous formulation of artemisinin.
A stock is available at St George's Hospital but, if there are problems, it is also available from UCLH.
Never delay treatment whilst obtaining Artesunate. Start quinine immediately in the first instance if awaiting a supply.

10.3. MANAGEMENT OF SUSPECTED TYPHOID FEVER

Primary source of recommendation:
BNF local practice
National / International Guidelines:
WHO diagnosis, prevention, and epidemic preparedness of typhoid fever 2003 and 2011
http://www.who.int/vaccine_research/documents/en/typhoid_diagnosis.pdf
http://apps.who.int/medicinedocs/documents/s20994en/s20994en.pdf

Recent good review of current epidemiology **and recent maps on resistance rates**:
Invasive Salmonella infections: Crump et al, Clinical Microbiology Reviews October 2015: 28 (4): 901-936 http://cmr.asm.org/content/28/4/901.full.pdf+html

Wain et al. Typhoid fever. Lancet. March 2015: 385 (9973), p1136-1145
DOI: http://dx.doi.org/10.1016/S0140-6736(13)62708-7

Typhoidal *Salmonella* serotypes
Salmonella species enterica serotype (serovar) typhi and paratyphi A, B or C are known as typhoidal *Salmonella* serotypes. They are human host-restricted organisms.
Typhoidal and paratyphoidal fever are collectively known as enteric fever.
Typhoid fever is potentially lethal. Typically, complications (GI bleeding, intestinal perforation, encephalopathy) arise from week 2 onwards in untreated patients.

Non-typhoidal *Salmonella*
Other *Salmonella* serovars (eg typhimurium, enteritidis etc) are grouped collectively as non-typhoidal *Salmonella*, they colonise/infect a broad range of vertebrate animals.
In the industrialised setting, they cause food poisoning, usually self-limited colitis. May cause invasion (bacteraemia) in the immunoscompromised or in the very young/very old.
In low and middle-income countries causes invasive disease in children and patients with HIV.

Initial Investigation
- At least two adequately filled blood culture sets
- Stool sample for MC&S (& ova, cysts and parasites)

Infection Control - Typhoid is a category 3 organism
- Inform Microbiology (on form) if Typhoid Fever is in differential diagnosis
- Remember to Notify CCDC – Check employment history / food handling

Treatment
- Consider resistance in patients on empirical treatment not improving
- Resistance is increasing and has a varied geographical distribution.
- Look for country-specific information. See the map in the Clin Micro Rev reference above as a starting point.

For example, *Salmonella typhi* multidrug-resistance (ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole) reaches 80% in some endemic areas. In India, ciprofloxacin resistance in 14-40% / azithromycin resistance in 7%, of the isolates (2012). Resistance to extended spectrum cephalosporins described in isolates from Germany, India and South East Asia.

Ciprofloxacin Sensitivity	Antibiotic / route	Dose	Duration
Severe / haemodynamically unstable			
Unknown or Resistant	Ceftriaxone IV	2g od	10-14 days (switch to PO azithromycin asap)
Quinolone-sensitive	Ciprofloxacin IV	400mg bd	10-14 days (switch to PO cipro asap)
Uncomplicated			
Unknown or Resistant	Azithromycin PO	500mg od	7 days
Quinolone-sensitive	Ciprofloxacin PO	500-750mg bd	7 days

10.4. MANAGEMENT OF NEUROCYSTICERCOSIS

Primary sources of recommendation:

Diagnostic/treatment guidelines:

Revised diagnostic criteria for neurocysticercosis. O.H. Del Brutto *et al*, *Journal of the Neurological Sciences* 2017; 372: 202-210 http://www.jns-journal.com/article/S0022-510X(16)30748-1/pdf

Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial. H.H. García *et al* Lancet Infectious Diseases 2014: 14 (8): 687-95 https://www.ncbi.nlm.nih.gov/pubmed/24999157

Useful reviews:

Neurocysticercosis: A Review. Del Brutto O.H. *ScientificWorldJournal* 2012: 159821 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3261519/

Clinical symptoms, diagnosis, and treatment of neurocysticercosis. Garcia HH, Nash TE, Del Brutto OH. *Lancet neurol.* 2014; 13: 1202-15 https://www.ncbi.nlm.nih.gov/pubmed/25453460

10.4.1 Diagnostic approach

Neurocysticercosis is infection of the brain with the larval parasite *Taenia solium*, the pig tapeworm, following ingestion of eggs by faecal-oral contamination from a human or animal host carrying the adult parasite in their guts. Hence, eating pork meat is NOT needed for acquiring this infection. It is the commonest acquired cause of epilepsy in the developing world.

Assess every patient individually. Diagnostic criteria are summarised in Del Brutto *et al* 2017 (link above). Cases are classified as 'definite' or 'probable' and other common causes should always be excluded. Each case should be discussed in a CIU/neuroradiology MDT. Useful investigations include:

- Assessment of risk factors: epidemiology, household contacts
- Brain imaging: CT, MRI, with contrast
- Serology for cysticercosis (Serum is more sensitive than CSF, but if CSF available, send that as well. Sensitivity is ~50-60% in single lesion disease and >95% where there are ≥2 live parasites.)
- Serology for: echinococcosis (hydatid); toxoplasmosis; strongyloides; HIV
- Lumbar puncture: protein/gluc, MC&S, AFB, cysticercal serology, Toxo PCR, cytology/cytospin
- Stools for OCP microscopy; screening of household contacts may be warranted particularly in cases of young children or where there is no known travel exposure
- Eye screen (to look for retinal cysts and/or anterior chamber cysts)
- XR thighs (to look for intra-muscular cysts)

Where further advice is needed, contact: Professor Peter Chiodini, Parasitology, HTD (0203 456 7891 x75809). Patients can be listed for discussion in their monthly Friday neuro-MDT.

Important differentials

TB, bacterial abscess, toxoplasmosis, CNS malignancy (lymphoma/glioblastoma/mets), multiple sclerosis, cystic hydatid disease (rare).

10.4.2 Management

Individualised care: Management decisions may take into consideration: the number and location of lesions; viability of the parasites (stage of cyst degeneration); individual patient factors e.g. co-morbidities; patient preference/social circumstances

Symptomatic management should guide the initial approach, particularly where there is raised ICP:

- ***Seizure control***: Treat seizures with an adequate dose of first-line anti-epileptic drugs. Ensure good seizure control prior to commencing anti-parasitic agents if possible.
- ***Surgery***: Cyst excision may be indicated if the cysts are very large or causing outflow obstruction. Intraventricular cysts should be managed by neuroendoscopy. Shunting may be required where there is hydrocephalus or ICH. Refer for a neurosurgical opinion where there is concern.
- Refer all patients to a neurologist.

Anti-parasitic treatment: This is <u>never</u> urgent.

- Calcified lesions do not require treatment. Viable lesions may resolve spontaneously, but the natural history of cyst involution is unpredictable and cysts may take years to degenerate. Existing data suggest that controlled killing may be safer; a watch-and-wait approach may occasionally be preferred.
- Where the decision to treat has been made, patients should be admitted due to risk of precipitating seizures. Admission may be done electively/semi-electively.
- Patients should remain in-patients for at least the first 7 days of anti-parasitic treatment, and ideally for the full duration. After 7 days, a risk assessment may be performed with the patient's consultant and supervised discharge may be considered.
- Dual anti-parasitic therapy (albendazole plus praziquantel) has been shown to be more effective than single agent therapy for multi-cystic disease. There is no evidence of superiority for single lesion disease, however the side effects are minimal and therefore use of dual agents may be justified.

10.4.3 Suggested treatment regimen

	Drug	Regimen	Route	Monitor	Comments
Anti-epileptic drugs	First-line AED e.g. Levetiracetam *Plus* Lorazepam *Or* Diazepam *Or* Midazolam	250mg OD initially, titrate upwards 4mg PRN 10mg PRN 10mg PRN	 IV IV Buccal		Stabilise prior to commencing anti-epileptic drugs if possible. PRN during inpatient treatment due to risk of provoked seizures. Give buccal Midazolam if no IV access
Steroids	Dexamethasone	0.1mg/kg/day in divided doses	PO	Glucose	Slow wean once anti-parastic treatment completed.
Anti-parasitic agents	Albendazole *Plus* Praziquantel	15mg/kg/d in 2 divided doses 50mg/kg/d in 2-3 divided doses	PO PO	 Praziquantel may lower serum levels of carbamazepine and phenytoin.	Commence anti-parasitic agents after minimum of 24h on steroids. Duration: 14 days.

- Warn pharmacy in advance as anti-parasitic drugs are not kept in stock.

- Always counsel the patient regarding:
    - Increased risk of seizures during treatment (hence need for inpatient treatment). Patients allowed off ward during their treatment as long as they are accompanied, and nursing staff are aware of their whereabouts.
    - Need for long-term anti-seizure drugs (usually at least 1-2 years) with weaning thereafter, as per neurology advice.
    - To inform DVLA and to not drive until cleared by a neurologist.
    - Possibility of treatment failure and need for re-treatment (up to 60%)
    - Possibility of misdiagnosis, particularly where serology is negative.

Follow-up post discharge

- Repeat MRI at e.g. 3 months to assess response to treatment / cyst resolution, and again if needed.
- If any changes in clinical condition, reconsider alternative diagnoses and repeat investigations where appropriate.
- Ensure patient has follow-up in neurology/epilepsy clinic.