GUIDELINES

For

GENERAL PRACTITIONERS

2024

Press record

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FOREWORD

It is a great honor for me to write a foreword to Guidelines for General Practitioners by General Practitioners' society, Myanmar Medical Association (Central).

General practitioners are the primary health providers in the community looking after the majority of the people of our country. They are being trusted and depend upon by every families in the surrounding area where they practice. The first and foremost care by the General Practitioners are the most important for all the people.

Guidelines based on a critical appraisal of scientific evidence (evidence-based guidelines) clarify which interventions are of proved benefit and document the quality of the supporting data. They alert clinicians to interventions unsupported by good science, reinforce the importance and methods of critical appraisal, and call attention to ineffective, dangerous, and wasteful practices.

Clinical guidelines can improve the quality of clinical decisions. They offer explicit recommendations for clinicians who are uncertain about how to proceed, overturn the beliefs of doctors accustomed to outdated practices, improve the consistency of care, and provide authoritative recommendations that reassure practitioners about the appropriateness of their treatment policies.

The Myanmar Medical Association together with the GP society has been helping out with the CME and CPD program for the Member doctors both inhouse sessions and online courses. This guideline is one of the essential parts of this CPD for the GPs.

I would like to congratulate the GP society for their effort for producing this guideline and also, I would like to encourage them to review and updated regularly.

Professor Aye Aung
President
Myanmar Medical Association

April, 2024

PREFACE

We are writing this letter to express our sincerest gratitude and appreciation for the successful completion of the **second edition** of the **General Practitioners' Guidelines**. This accomplishment is the result of an exceptional collaborative effort, and we would like to extend our thanks to all those involved.

The General Practitioners' Guidelines has been an invaluable resource since its inception with the launch of the first edition in November 2017. As per the initial plan, the guidelines were intended to be updated every three years to ensure the most up-to-date information reaches Myanmar General Practitioners, enhancing their knowledge in primary healthcare and family health.

However, the unforeseen outbreak of the Covid-19 pandemic disrupted our plans and posed numerous challenges for the team. In-person meetings became impossible due to safety concerns, making it necessary for us to find alternative means of communication and collaboration. Despite the adversity faced, the team members demonstrated remarkable resilience and adaptability by utilizing online platforms and technology to continue the update process.

We would like to extend our deepest gratitude to the dedicated team members who persevered and worked tirelessly during these trying times. Their commitment, professionalism, and unwavering dedication to the project enabled us to overcome the obstacles posed by the pandemic and successfully complete the second edition of the guideline.

Furthermore, we would like to express our sincere appreciation to the specialist societies that actively contributed to the development of the guidelines. Their expertise and invaluable insights have ensured that the content remains current, accurate, and relevant, enabling our General Practitioners to provide the highest quality of care to their patients.

We would also like to extend our heartfelt thanks to the esteemed President of the Myanmar Medical Association, for their continuous support and guidance throughout this endeavor. Their leadership and unwavering commitment to advancing medical knowledge in Myanmar have been instrumental in the success of this Guidelines.

Moreover, the decision to distribute the guideline as electronic copies reflects our commitment to ensuring easy access for all Myanmar General Practitioners. By making it available in this format, we aim to facilitate the dissemination of updated knowledge, thus empowering our healthcare professionals to deliver the best possible care to the community.

In conclusion, we would like to express our deepest gratitude to all those who contributed to the development and distribution of the General Practitioners' Guidelines Second Edition. The unwavering supports and collective efforts have made a significant impact on enhancing primary healthcare and family health care in Myanmar.

Once again, thank you for your outstanding dedication, resilience, and invaluable contributions. We look forward to our continued collaboration in advancing medical knowledge and improving healthcare outcomes for all.

Dr Khine Soe Win and Dr Win Zaw April, 2024
General Practitioners' Society (Central)
Myanmar Medical Association

EDITORIAL

It is my privilege to inform you that our updated and revised edition of "**Guidelines for General Practitioners**" will be published very soon and it is my great pleasure to be the editor-in-chief of this guideline book. There are various reasons for revising and updating the previous edition.

This is the fact that some important topics, for example, malaria and family violence are missing in the first edition and some clinical practice guidelines like Diabetes Management have been changed during the interim period. Of course, this opportunity arises due to the emergence of COVID-19 in the world. As all you know, Medicine is an ever-changing science; we need to consider updating our guidelines at least five- yearly. Hence the time is up now!

Education is achieved by assimilating information from many resources and readers of this book can enhance their learning experience in terms of reflecting in their daily Family/General Practice. We all take immerse pride in contributing good educational resource dedicated to Myanmar General Practitioners. The editors and authors anticipate that the readers will both enjoy and profit from their work in preparing this volume.

Happy studying and learning,

Dr Win Lwin Thein
Editor-in chief
Vice President (GP Society)
April, 2024

ACKNOWLEDGEMENT

We would like to thank all our talented and hard-working colleagues who have contributed to the ongoing development of the **Guidelines for General Practitioners**.

Especially, we would like to highlight the significance of the second edition which appears when the family medicine development process in Myanmar is being idle. Many factors are impeding the developing process lately, which has been accelerated previously by the commitment of the MOHS, the medical universities, and the General Practitioners' Society before the COVID-19 pandemic started.

No one can deny that the Myanmar health care system is lacking a strong and effective primary care task force. The best solution to mend this defect is retraining the thousands of general practitioners who are working individually across the country. Here comes the role of family medicine to train these GPs and primary care doctors to be able to use its principles effectively and, in turn, strengthen primary care.

Many GPs are using some family medicine principles consciously or unconsciously in varying degree of competency. Person-centered care, continuity of care, and family-oriented care became the culture of most practices for a long time. But only a few GPs can enjoy the most effective coordinated care and seamless continuity of care with secondary and tertiary care providers. The reasons behind this would be the absence of standardization in general practitioners' service quality and unawareness of the value of family medicine practitioners by other specialties and the public.

To resolve this ambiguity, primary care doctors should be involved in the retraining programs and thereafter CME/CPD and other life-long-learning programs which prescribe family medicine curricula.

We also acknowledge the effort of the contributors to make this new edition more family medicine-oriented, in addition to the Family Medicine chapter at the beginning of the book. We genuinely believe that the new edition will be a better reference for the GP/FP who wants to practice quality primary care and for future family medicine programs in Myanmar.

Finally, we would like to thank all academic writers who contributed to the General Practice Guidelines-first edition. Without their kind support, this second edition could never have happened.

Regards,

Dr. Tin Aye and Dr. Kyaw Thu

General Practitioners' Society (Central), MMA **April, 2024**

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SYMBOLS AND ABBREVIATIONS

AAA abdominal aortic aneurysm
ABC airway, breathing, circulation
ABCD airway, breathing, circulation, dextrose
ABO A, B and O blood groups
ACE angiotensin-converting enzyme
ACEI angiotensin-converting enzyme inhibitor
ACTH adrenocorticotrophic hormone
ADHD attention deficit hyperactivity disorder
ADT adult diphtheria vaccine
AFP alpha-fetoprotein
AI aortic incompetence
AIDS acquired immunodeficiency syndrome
AIIRA angiotensin II (2) reuptake antagonist
AKF acute kidney failure
ALE average life expectancy
ALL acute lymphocytic leukaemia
ALP alkaline phosphatase
ALT alanine aminotransferase
AMI acute myocardial infarction
AML acute myeloid leukaemia
ANA antinuclear antibody
ANF antinuclear factor
AP anterior–posterior
APH ante-partum haemorrhage
ASD atrial septal defect
ASIS anterior superior iliac spine
ASOT antistreptolysin O titre
AST aspartate aminotransferase
AV atrioventricular
AZT azidothymidine
BCC basal cell carcinoma
BCG bacille Calmette-Guérin
BMD bone mass density
BMI body mass index
BP blood pressure
BPH benign prostatic hyperplasia
Ca carcinoma
CABG coronary artery bypass grafting
CAD coronary artery disease
CAP community acquired pneumonia
CBT cognitive behaviour therapy
CCF congestive cardiac failure
CCU coronary care unit
CD4 T helper cell
CD8 T suppressor cell
CDT combined diphtheria/tetanus vaccine
CEA carcinoembryonic antigen
CFS chronic fatigue syndrome
CHD coronary heart disease
CHF chronic heart failure
CIN cervical intraepithelial neoplasia
CK creatinine kinase
CKD chronic kidney disease
CKF chronic kidney failure
CML chronic myeloid leukaemia
CMV cytomegalovirus
CNS central nervous system
COAD chronic obstructive airways disease
COC combined oral contraceptive
COCP combined oral contraceptive pill
COPD chronic obstructive pulmonary disease
COX cyclooxygenase
CPA cardiopulmonary arrest
CPAP continuous positive airways pressure
CPK creatine phosphokinase
CPR cardiopulmonary resuscitation
CR controlled release
CREST calcinosis cutis; Raynaud's phenomenon; oesophageal involvement; sclerodactyly; telangiectasia
CRF chronic renal failure
CR(K)F chronic renal (kidney) failure
CRP C-reactive protein
CSF cerebrospinal fluid
CT computerised tomography
CTS carpal tunnel syndrome
CVA cerebrovascular accident
CVS cardiovascular system
CXR chest X-ray
DBP diastolic blood pressure
DC direct current
DHA docosahexaenoic acid
DI diabetes insipidus
DIC disseminated intravascular coagulation
dL decilitre
DMARDs disease modifying antirheumatic drugs
DNA deoxyribose-nucleic acid
DRABC defibrillation, resuscitation, airway, breathing, circulation
drug dosage bd—twice daily, tid/tds -three times daily, qid/qds -four times daily
ds double strand
DS double strength
DSM diagnostic and statistical manual (of mental disorders)
DU duodenal ulcer
DUB dysfunctional uterine bleeding
DVT deep venous thrombosis
EBM Epstein-Barr mononucleosis (glandular fever)
EBV Epstein-Barr virus
ECG electrocardiogram
ECT electroconvulsive therapy
EDD expected due date
EEG electroencephalogram
ELISA enzyme linked immunosorbent assay
ESRF end-stage renal failure
ESR(K)F end stage renal (kidney) failure
ERCP endoscopic retrograde cholangiopancreatography
esp. especially
ESR erythrocyte sedimentation rate
FB foreign body
FBE full blood count

FEV1 forced expiratory volume in 1 second
fL femtolitre = (1e–15) litre
FSH follicle stimulating hormone
FUO fever of undetermined origin
FVC forced vital capacity
g gram
GA general anaesthetic
GABHS group A beta-haemolytic streptococcus
GBS Guillain-Barré syndrome
GFR glomerular filtration rate
GI glycaemic index
GIT gastrointestinal tract
GLP glucagon-like peptide
GnRH gonadotrophin-releasing hormone
GO gastro-oesophageal
GORD gastro-oesophageal refl ux
GP general practitioner
G-6-PD glucose-6-phosphate
GU gastric ulcer
HAV hepatitis A virus
anti-HAV hepatitis A antibody
Hb haemoglobin
HbA haemoglobin A
anti-HBc hepatitis B core antibody
HBeAg hepatitis B e antigen
anti-HBs hepatitis B surface antibody
HBsAg hepatitis B surface antigen
HBV hepatitis B virus
HCG human chorionic gonadotropin
HCV hepatitis C virus
anti-HCV hepatitis C virus antibody
HDL high-density lipoprotein
HEV hepatitis E virus
HFM hand, foot and mouth
HFV hepatitis F virus
HGV hepatitis G virus
HIV human immunodeficiency virus
HNPCC hereditary nonpolyposis colorectal cancer
HPV human papilloma virus
HRT hormone replacement therapy
HSV herpes simplex viral infection
IBS irritable bowel syndrome
ICE ice, compression, elevation
ICS inhaled corticosteroid
ICS intercondylar separation
ICT immunochromatographic test
IDDM insulin dependent diabetes mellitus
IDU injecting drug user
IgE immunoglobulin E
IgG immunoglobulin G
IgM immunoglobulin M
IHD ischaemic heart disease
IM, IMI intramuscular injection
inc. including
IPPV intermittent positive pressure variation
IR internal rotation
ITP idiopathic (or immune) thrombocytopenia purpura
IUCD intrauterine contraceptive device
IUGR intrauterine growth retardation
IV intravenous
IVI intravenous injection
IVP intravenous pyelogram
IVU intravenous urogram
JCA juvenile chronic arthritis
JVP jugular venous pulse
KA keratoacanthoma
kg kilogram
KOH potassium hydroxide
LA local anaesthetic
LABA long acting beta agonist
LBBB left branch bundle block
LBO large bowel obstruction
LBP low back pain
LDH/LH lactic dehydrogenase
LDL low-density lipoprotein
LFTs liver function tests
LH luteinising hormone
LHRH luteinising hormone releasing hormone
LIF left iliac fossa
LMN lower motor neurone
LNG levonorgestrel
LRTI lower respiratory tract infection
LSD lysergic acid
LUQ left upper quadrant
LUTS lower urinary tract symptoms
LV left ventricular
LVH left ventricular hypertrophy
mane in morning
MAOI monoamine oxidase inhibitor
mcg microgram (also µg)
MCV mean corpuscular volume
MDI metered dose inhaler
MDR multi-drug resistant TB
MI myocardial infarction
MRCP magnetic resonance cholangiography
MRI magnetic resonance imaging
MS multiple sclerosis
MSM men who have sex with men
MSU midstream urine
N normal
NAD no abnormality detected
NGU non-gonococcal urethritis
NHL non-Hodgkin's lymphoma
NIDDM non-insulin dependent diabetes mellitus
nocte at night
NSAIDs non-steroidal anti-inflammatory drugs
NSU non-specific urethritis
(o) taken orally
OA osteoarthritis
OCP oral contraceptive pill
OGTT oral glucose tolerance test
OSA obstructive sleep apnoea
OTC over the counter
PA posterior–anterior
PAN polyarteritis nodosa
Pap Papanicolaou
pc after meals
PCA percutaneous continuous analgesia
PCB post coital bleeding

PCL posterior cruciate ligament
PCOS polycystic ovarian syndrome
PCP pneumocystis carinii pneumonia
PCR polymerase chain reaction
PCV packed cell volume
PDA patent ductus arteriosus
PEF peak expiratory flow
PEFR peak expiratory flow rate
PET pre-eclamptic toxaemia
PFT pulmonary function test
PH past history
PID pelvic inflammatory disease
PLISSIT permission: limited information: specific suggestion: intensive therapy
PMS premenstrual syndrome
PMT premenstrual tension
POP plaster of Paris
POP progestogen-only pill
PPI proton-pump inhibitor
PPROM preterm premature rupture of membranes
PR per rectum
prn as and when needed
PROM premature rupture of membranes
PSA prostate specific antigen
PSIS posterior superior iliac spine
PSVT paroxysmal supraventricular tachycardia
PT prothrombin time
PTC percutaneous transhepatic cholangiography
PU peptic ulcer
PUO pyrexia of undetermined origin
pv per vagina
qds, qid four times daily
RA rheumatoid arthritis
RBBB right branch bundle block
RBC red blood cell
RCT randomised controlled trial
RF rheumatic fever
Rh rhesus
RIB rest in bed
RICE rest, ice, compression, elevation
RIF right iliac fossa
RPR rapid plasma reagin
RR relative risk
RSV respiratory syncytial virus
RT reverse transcriptase
rtPA recombinant tissue plasminogen activator
SAH subarachnoid haemorrhage
SARS severe acute respiratory distress syndrome
SBE subacute bacterial endocarditis
SBO small bowel obstruction
SBP systolic blood pressure
SC/SCI subcutaneous/subcutaneous injection
SCC squamous cell carcinoma
SCG sodium cromoglycate
SIADH syndrome of secretion of inappropriate antidiuretic hormone
SIDS sudden infant death syndrome
SIJ sacroiliac joint
SL sublingual
SLE systemic lupus erythematosus
SLR straight leg raising
SND sensorineural deafness
SNHL sensorineural hearing loss
SNRI serotonin noradrenaline reuptake inhibitor
SOB shortness of breath
sp species
SR sustained release
SSRI selective serotonin reuptake inhibitor
SSS sick sinus syndrome
stat at once
STI sexually transmitted infection
SVC superior vena cava
SVT supraventricular tachycardia
T3 tri-iodothyronine
T4 thyroxine
TB tuberculosis
tds, tid three times daily
TENS transcutaneous electrical nerve stimulation
TFTs thyroid function tests
TG triglyceride
TIA transient ischaemic attack
TIBC total iron binding capacity
TM tympanic membrane
TMJ temporomandibular joint
TNF tissue necrosis factor
TOF tracheo-oesophageal fistula
TORCH toxoplasmosis, rubella, cytomegalovirus, herpes virus
TPHA Treponema pallidum haemoglutination test
TSE testicular self-examination
TSH thyroid-stimulating hormone
TT thrombin time
TV tidal volume
U units
UC ulcerative colitis
U & E urea and electrolytes
µg microgram
UMN upper motor neurone
URTI upper respiratory tract infection
US ultrasound
UTI urinary tract infection
U ultraviolet
VC vital capacity
VDRL Venereal Disease Reference Laboratory
VF ventricular fibrillation
VMA vanillyl mandelic acid
VSD ventricular septal defect
VT ventricular tachycardia
VUR vesico-ureteric reflux
VWD von Willebrand's disease
WBC white blood cells
WCC white cell count
WHO World Health Organization
WPW Wolff-Parkinson-White
XL sex linked

CHAPTER (14) INFECTIONS AND INFESTATION PROBLEMS

Guide to Antibiotic Prescribing

Human Immunodeficiency Viral Infection

Tuberculosis

Malaria

Sexually Transmitted Diseases

Hepatitis B Infection

Hepatitis C Infection

Covid 19

Helminthiasis

GUIDE TO ANTIBIOTIC PRESCRIBING

For prevention of antimicrobial resistant infection, we must follow the guideline of prescribing antimicrobial agents.

DO NOT PRESCRIBE ANTIBIOTICS IN THE ABSENCE OF CLINICAL EVIDENCE OF BACTERIAL INFECTION, OR FOR A SELF-LIMITING CONDITION

- whey and antibiotics is not the best option
- alternative options, e.g. symptomatic treatment, delayed prescribing
- the views and expectations of the patients
- safety-netting advice: what the patient should do if their condition deteriorates.

Empirical treatment

Before prescribing empirical antibiotics

- Clinician should first determine whether antimicrobial therapy is warranted for a given patient
- Is antimicrobial agents indicated on the basis of clinical finding?
- Is it prudent to wait until such clinical findings become apparent?
- Can some simple bedside tests done to confirm your suspicion? (Microscopy, Gram staining)
- What are the likely aetiologic agents for the patient's illness?
- Is there clinical evidence (from clinical trials) that antimicrobial therapy will confer clinical benefit for the patients? (Evidence-based Medicine)

Definitive treatment

- Can a narrower spectrum agent be substituted for initial empiric drug?

Prophylactic treatment

Take microbiological samples before prescribing

especially for:

- hospital in-patient: review your prescription as soon as MC&S result is available
- recurrent or persistent infection
- non-severe infection: consider if your prescription can wait for MC&S results

Follow local guidelines first

- Best practice is informed by local epidemiology and sensitivities.

Consider benefit and harm for each individual patient

- Allergies: clarify that patient's reaction – the true incidence of penicillin allergy in patients who report that they are allergic is <10%. In those with a confirmed penicillin allergy, corss-reactivity with 3rd generation cephalosporins and carbapenems is possible but rare (<1%)
- Dose adjust for renal function and weight: use ideal body weight in extremes of BMI (or ideal weight plus a % of excess weight – see local guidelines)
- Check for medication interactions
- In pregnancy and lactation

Prescribe the shortest effective course.

- Most antibiotics have good oral availability. Use IV antibiotics only if in line with local and national (sepsis) guidelines.

Route of administration

- The route of administration an antibacterial often depends on the severity of the infection.
- Life threatening infections require intravenous therapy.
- Antibacterials that are well absorbed, may be given by mouth even for some serious infections.
- Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate.

Duration of therapy

- Duration of therapy depends on the nature of the infection and the response to treatment (can be assessed by procalcitonin level).
- Courses should not be unduly prolonged because they encourage resistance, they may lead to side-effects and they are costly.
- However, in certain infections such as tuberculosis or osteomyelitis it may be necessary to treat for prolonged periods.
- Conversely a single dose of an antibacterial may cure uncomplicated urinary tract infections. The prescriptions for an antibacterial should specify the duration of treatment or the date when treatment is to be reviewed.
- Then focus: review the clinical diagnosis and continuing need for antibiotics at 48 hr for all in-patients and all patients prescribed IV antibiotics:
    - Stop antibiotics if there is no evidence of infection
    - Switch from IV to oral whenever possible
    - Change to a narrow spectrum antibiotic whenever possible
    - Continue regular clinical review whilst antibiotics are prescribed

Reference:

1. *Zaw Lynn Aung, Antimicrobial Resistant-Rational antibiotic therapy, 20-1-2018, MOHS*

HUMAN IMMUNODEFICIENCY VIRAL INFECTION
HUMAN IMMUNO-DEFICIENCY VIRUS

- HIV is a virus that causes Acquired Immune Deficiency Syndrome (AIDS). The first virus was called HIV1 and the second virus was called HIV2.
- HIV is a retro virus infecting T- helper cells bearing CD4 receptor, which contains RNA in his core; the virus itself is surrounded by a protein and lipid envelope. To replicate itself in the human cells, the virus first selects and attaches cell carrying a special receptor known as CD4 antigen.

How does HIV replicate?

- Once HIV enters the human body, it specifically seeks out a particular type of T –lymphocyte in the blood, called the CD4 T-lymphocyte. The various stages of HIV replication are explained below:
    - HIV enters a CD4 cell.
    - HIV is a retrovirus, meaning that its genetic information is stored on single-stranded RNA instead of the double-stranded DNA found in most organisms. To replicate, HIV uses an enzyme known as reverse transcriptase to convert its RNA into DNA.
    - HIV DNA enters the nucleus of the CD4 cell and inserts itself into the cell's DNA. HIV DNA then instructs the cell to make many copies of the original virus.
    - With the help of the protease enzyme, new virus particles are assembled. These newly formed virus leaves the cell, ready to infect other CD4 cells.

What is "Primary HIV Infection"?

- The term "Primary HIV Infection" (also called "acute HIV INFECTION") refers to the illness which occurs when HIV first infects an individual. This stage is characterized by non- specific flu-like symptoms such as fever, lethargy, sore throat, malaise, rash, lymphadenopathy, arthralgia, myalgias, headaches and rarely meningitis. These symptoms usually occur within 2-6 weeks after acquiring the virus. Most symptoms usually resolve within 2- 3 weeks.
- Within 2 to 4 weeks after the initial infection, high levels of virus are present in the blood.
- The immune system now begins to recognize the virus and produce antibodies.
- HIV antibodies can be detected in the blood usually within 1- 3 weeks after symptoms appear.
- The time period during which the individual is infected with HIV, but has no antibodies in his blood, is called the 'window period". During the window period, the HIV – infected person is capable of transmitting the virus to others, and is infectious. This phase of primary HIV infection is also called the "acute seroconversion syndrome". The term "seroconversion" refers to the appearance of HIV antibodies in the blood. During the window period, the ELISA test will give a negative result; the only test for detecting HIV infection at this stage is the PCR test.

What is the difference between HIV infection and AIDS?

- It is important to distinguish between being infected with HIV and having AIDS. People infected with HIV may take 10 years before they develop AIDS. Acute HIV syndrome, associated with seroconversion of HIV can occur as early as few weeks after a person is infected. The person may be asymptomatic or develop" flu like symptoms and signs' The period before the development of an antibody response- usually between 6-12 weeks-is often referred to as the window period when a person is infectious but not positive in HIV antibody test.
- HIV infection
    - After primary infection, there is a long asymptomatic phase, which may last for several years. Thus, the patient who is infected with HIV, but is asymptomatic or mildly symptomatic, is referred to as "HIV positive". During this phase, the virus is actively

multiplying and destroying the CD4 cells.

- AIDS
    - When the CD4 cells decrease to 200cells/µl, or the patient starts suffering from a characteristic range of severe opportunistic infections (AIDS-define illnesses), he is said to be suffering from AIDS. It may take 8-10 years to reach this stage, although this may vary between patients.
    - Thus, AIDS represents an advanced stage of HIV infection, when the patient suffers from a characteristic range of opportunistic infections.

What is the natural history of HIV infection?

- HIV attacks the CD4 T- lymphocytes
- HIV has a special affinity for the CD4 T-lymphocyte. It multiplies rapidly and continuously within these cells. Although the body does replace the lostCD4 cells, the rate of destruction of the CD4 cells far exceeds the body's ability to replace them. Thus, as HIV infection progresses, there is a progressive decline in the number of CD4 T-lymphocytes. The CD4 count may drop to as low as 50 cells/ul or even lower, from the normal level of about 1000 cells/µl.
- **HIV infection leads to immunodeficiency.**
    - HIV destroys the CD4 cells, which play a vital role in immune function. The loss of CD4 cells leads to immunodeficiency in HIV-infected patients. In other words, these patients become susceptible to a variety of "opportunistic infections". Opportunistic infections are commonly encountered when the CD4 count is less than 200 cells/µl. The lower the number of CD4 cells, the more advanced is the stage of disease. Thus, HIV causes a progressive and irreversible destruction of immune system. Opportunistic infections occur due to the immune destruction caused by the virus.
- **Immunodeficiency cause opportunistic infections**
    - As the immune function declines, the HIV- positive patient is plagued by variety of opportunistic infections. Virtually no system or organ is spared. Moreover, as immunodeficiency increases, these infections become more difficult to treat, and have a greater tendency to relapse.
- **Immunodeficiency leads to death,**
    - If an HIV-positive patient is left untreated, over the years, his CD4 cells will continue to decline progressively, immune function will deteriorate, and ultimately, he would die because of the opportunistic infections that ravage his body.
- **Common opportunistic infections**
    - Tuberculosis, both pulmonary as well as extrapulmonary.
    - Oral candidiasis
    - Oesophageal candidiasis
    - Herpes zoster
    - Diarrhea, which may be due to a variety of pathogen:
        - Protozoral- amoeba, Giardia,
        - Cryptosporidium,
        - Helminth- Strongyloides,
        - Viral- Cytomegalovirus
    - Bacterial pneumonia and Pneumocystis carinii pneumonia
    - Toxoplasma encephalitis
    - Cryptococcal meningitis
    - Cytomegalovirus retinitis (CMV)
    - Cancers such as Kaposi's sarcoma and non-Hodgkin's lymphoma

Modes of transmission

- HIV is transmitted through unprotected sexual intercourse (anal or vaginal), transfusion of contaminated blood, sharing of contaminated needles, and between a mother and her infant

during pregnancy, childbirth and breastfeeding.

- HIV does not survive long outside the human body and it cannot be transmitted by air or water, insects including mosquito bites, saliva, tears or sweat, causal contact like shaking hands, sharing toilets or household utensils.

So, HIV is transmitted by the following routes:

- Sexual transmission
- Transfusion of infected blood and blood products
- Maternal transmission
- HIV –contaminated instruments

Which tests are used to diagnose HIV infection?

- Test which are commonly used to diagnose HIV infection are:
- ELISA:
  - This is the initial, or screening, test for HIV infection. It tests for the present of antibodies against HIV in the blood. A positive result is usually obtained within 3 months of acquiring the infection.
- Western Blot:
  - This is a confirmatory test. It detects antibodies against antigens coded by 3 different viral antigens. There are various criteria for a positive Western Blot. As per the WHO criteria, a positive Western Blot is defined as the presence of any two of the p24gp41 and gp12/gp160 bands. The presence of all bands is considered a negative test.
- Polymerase chain reaction (PCR) assays:
  - The PCR technique is used to assay for both HIV RNA and HIV DNA. The only test to diagnose HIV infection in window period is the HIV DNA PCR. The HIV RNA PCR test can measure the amount of HIV RNA in the blood (also referred to as the "viral load". The viral load indicates the rate of disease progression, with higher viral loads predicted of faster disease progression. HIV RNA PCR is also used to assess the response to anti-HIV therapy.
- WHO recommends 3 positive rapid tests as a confirmation of HIV diagnosis. The most commonly used 3 rapid tests (in Myanmar) are:
  - **Determine** (test 1),
  - **Unigold** (test2) and
  - **Stat Pak** (test 3);
  - the first being 99. 9% sensitive and the last 2 being 100% specific.
- The interval between " confirmation" and "verification" can be as close as a few days, in a patient starting ART rapidly. The individuals who test HIV reactive should be referred immediately to the nearest site approved or confirmatory testing to confirm their HIV status. . Approved sites for testing to confirm HIV status can be a community site, or health facility. or certified laboratory, or a health facility which provides ART.

Recognition of Symptomatic HIV infection

- Suggestive clinical findings:
  - Fever of more than one month's duration
  - Weight loss of more than 10%
  - Diarrhea of more than one month's duration
  - Mucocutaneous manifestations
  - Generalised lymphadenopathy (extra-inguinal)
  - Infections, severe or recurrent
    - Past or present multidermatomal herpes zoster
    - Hairy leukoplakia
    - Warts

        - Molluscum contagiosum
        - Oral thrush
        - Papulonecrotic lesion
        - Folliculitis
        - Vulvovaginitis
    - Others
        - Severe recurrent seborrheic dermatitis
        - Chronic prurigo
        - Reiter's syndrome
        - Kaposi 's sarcoma
        - Unexplained neurological manifestations (seizures, motor or sensory deficits, dementia and progressive headache
        - Chronic cough more than one month's duration or unexplained respiratory distress
        - Cytomegalovirus retinitis
        - Extrapulmonary pulmonary or disseminated and extensive pulmonary tuberculosis
        - Recurrent pneumonia
        - Invasive cervical carcinoma

WHO clinical case definition for AIDS

- Clinical AIDS in an adult is defined as an individual who has been identified as meeting the two criteria A and B below:
    - **Positive test for HIV infection by two tests based on preferably two different antigens:**
    - **Any one of the following criteria:**
        - Weight loss of 10% body weight or cachexia, not known to be due to a condition unrelated to HIV infection
        - Chronic diarrhea of one month's duration, intermittent or constant
        - Disseminated, military or extrapulmonary tuberculosis
        - Candidiasis of the oesophagus; diagnosable as dysphagia, odynophagia and or candidiasis
        - Neurological impairment restricting daily activities, not known to be due to a condition unrelated to HIV (trauma)
        - Kaposi's sarcoma

Clinical staging

- Recently WHO classifies patients as those with advanced disease (WHO stage 3 or 4 disease and/or CD4 <200 cells/ml) and those who are clinically well; such individuals may be ART naive or have interrupted treatment.

WHO clinical staging of HIV disease in adults, adolescents and children

Adults and Adolescents	Children
Clinical stage 1	
• Asymptomatic • Persistent generalized lymphadenopathy	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2	
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) • Herpes zoster	• Unexplained persistent hepatosplenomegaly • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) • Herpes zoster

• Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrhoeic dermatitis • Fugal nail infections	• Lineal gingival erythema • Recurrent oral ulceration • Papular pruritic eruption • Fungal nail infection • Extensive wart virus infection • Extensive molluscum contagiosum • Unexplained persistent parotid enlargement
Clinical stage 3	
• Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhoea for >1 month • Unexplained persistent fever (intermittent or constant for >1 month) • Persistent oral candidiasis • Oral hairy leukoplakia • Pulmonary tuberculosis • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9/l) and/ or chronic thrombocytopaenia (<50 x 10^9/l)	• Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5°C, intermittent or constant, for >1 month) • Persistent oral candidiasis (after first 6 weeks of life) • Oral hairy leukoplakia • Lymph node TB • Pulmonary TB • Severe recurrent bacterial pneumonia • Acute necrotizing ulcerative gingivitis or periodontitis • Unexplained anaemia (<8.0 g/dl), neutropaenia (<0.5 10^9/l) or chronic thrombocytopaenia (<50 10^9/l) • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4	
• HIV wasting syndrome • *Pneumocystis jirovecii* pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary TB • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Extrapulmonary cryptococcosis, including meningitis • Disseminated non-tuberculous mycobacterial infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis • Chronic isosporiasis	• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • Pneumocystis jirovecii pneumonia • Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) • Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary TB • Kaposi sarcoma • Cytomegalovirus infection; retinitis or infection of other organs with onset at age older than 1 month • Central nervous system toxoplasmosis (after the neonatal period) • HIV encephalopathy

• Penicilliosis • Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) • Lymphoma (cerebral or B-cell non- Hodgkin) • Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy • Recurrent septicaemia (including nontyphoidal Salmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis	• Extrapulmonary cryptococcosis, including meningitis • Disseminated non-tuberculous mycobacterial • infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) • Cerebral or B-cell non-Hodgkin lymphoma • HIV-associated cardiomyopathy or nephropathy

- For children younger than 5 years, moderate malnutrition is defined as weight-for-height ≤2 z-score or mid-upper arm circumference ≥115 mm to <125 mm.
- For children younger than 5 years of age, severe wasting is defined as weight-for-height ≤3 z-score; stunting is defined as length-for-age/height-for-age ≤2 z-score; and severe acute malnutrition is either weight for height ≤3 z-score or mid-upper arm circumference <115 mm or the presence of oedema.

Initial Clinical Management

- The HIV "test and treat" policy to all people diagnosed with HIV. The "test and treat" policy involves providing lifelong ART to people living with HIV irrespective of CD4 or WHO HIV clinical staging. ART should be initiated at the earliest opportunity in all people with confirmed HIV infection, regardless of clinical stage or CD4 cell count.

ANTIRETROVIRAL THERAPY FOR PEOPLE LIVING WITH HIV THE GOAL OF ART

- The aim of antiretroviral therapy is to suppress viral load levels amongst PLHIV to undetectable levels, reduce the risk of morbidity
- and mortality associated with HIV, and reduce transmission of HIV.
- ART should be initiated at the earliest opportunity in all people with confirmed HIV infection, regardless of clinical stage or CD4 cell count.
- The guidelines update recommends the use of Dolutegravir, a newer drug, in combination with Tenofovir and Lamivudine as preferred first-line drug for eligible people living with HIV.
- In practice, while the HIV diagnostic tests, baseline investigations and co-infection diagnosis and OI screening investigations are process, the patient is offered CPT (co-trimoxazole prophylaxis therapy) which is 2 tablets of single strength (480mg) or one tablet of double strength (960mg) Septrin daily.

Cotrimoxazole prophylaxis

- Cotrimoxazole prophylaxis is an important part of the management of people living with HIV. It is recommended for adult including pregnant women with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with CD4 count of <350/mm³. One double-strength tablet daily of Cotrimoxazole daily is recommended (sulfamethoxazole 800 mg/ trimethoprim 160 mg = 960 mg).
- Skin reaction is the commonest side effect with Cotrimoxazole. Other side effects are bone marrow toxicity and hepatotoxicity. Side effects can be monitored clinically. However, these drug-related adverse effects are not common and typically occur within the first few weeks of starting prophylaxis. Clinical monitoring is usually sufficient. The safety of Cotrimoxazole in long-term use has been established.

- Dapsone 100 mg a day may be used if there is hypersensitivity to Cotrimoxazole, but Dapsone is less effective than Cotrimoxazole. If there is hypersensitivity to both Cotrimoxazole and Dapsone, it may be possible to carry out Cotrimoxazole desensitization under careful supervision. Both Cotrimoxazole and Dapsone can cause intravascular haemolysis in patients with G6PD deficiency and should not be prescribed if the patient is known to be enzyme deficient.

Baseline Investigations

- Investigations done before staring ART are: CD4, STS, HBsAg, HCV antibody, CBC, Serum creatinine and e GFR LFT, HB.

Counseling sessions

- comprise of pretest, post-test, follow-up adherence counseling and ART counseling which can be spread over two or three visits. In the 3rd visit, verification result is available. Follow-up adherence and ART adherence counseling are done and ART is initiated.

What is the treatment approach for an HIV-positive patient?

- Basically, the treatment of an HIV-infected patient involves:
    - Inhibiting the replication of the virus using antiretrovirals
    - Treatment and prophylaxis of opportunistic infections.
    - Psychosocial support

What does antiretroviral therapy do?

- Antiretroviral therapy helps in:
    - Preserving immune function
    - Preventing disease progression
    - Reducing the incidence of opportunistic infections
    - Prolonging survival
    - So antiretroviral therapy has been proven to be effective in:
    - Decreasing viral load, increasing CD4 counts, decreasing the incidence of opportunistic infections, preventing disease progression and improving quality of life.

Classification of antiretrovirals

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	250-300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400-600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily

Proteases inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg daily a or 600 mg + 100 mg twice daily
Lopinavir + ritonavir (LPV/r)	400 mg/100 mg twice daily
	Consideration for individuals receiving TB therapy In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r: (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg +RTV 400 mg twice daily)
Integrase strand transfer inhibitors (InSTIs)	
Dolutegravir (DTG)	50 mg once daily In the presence of rifampicin, adjust the dosage of DTG as 50 mg twice daily
Raltegravir (RAL)	400 mg twice daily

ART regimens for Adults

First line ART	Second line ART	Third line ART
Tenofovir + Lamivudine + Efavirenz	Zidovudine + Lamivudine + Dolutegravir	Boosted Darunavir + INSTI+NRTI
Tenofovir + Lamivudine + Dolutegravir	Zidovudine + Lamivudine + Efavirenz	Boosted Darunavir + INSTI+NRTI

- HBP coinfected patients should always receive TDF regimen.
- Patients with significant anaemia should avoid Zidovudine.

RECOMMENDED FIRST-LINE REGIMEN FOR INITIATING ART IN ADULTS AND ADOLESCENTS

- AGED ≥10 AND ≥35kg
- All eligible HIV-infected adults and adolescents ≥10 years and weighing ≥ 35kg should be initiated on tenofovir, lamivudine and
- Dolutegravir (TDF+3TC+DTG) as a once-daily fixed dose combination with the exception of: Women and adolescent girls of child bearing potential that are pregnant, intend to become pregnant or are not on effective contraception

RATIONALE FOR USING DOLUTEGRAVIR (DTG)

a. **High Circulating levels of resistance to NNRTI-containing First-line Therapy**
NNRTI-containing combinations have been used as first-line regimens for adults

b. ***Superior Efficacy over Current Standard of Care Regimens***
DTG is superior to alternative ARV options and patients can experience rapid viral suppression, thereby reducing risk of transmitting HIV while prolonging time on first-line treatment. It has been shown that patients who receive DTG achieve viral suppression faster as compared to those who receive EFV.

c. ***Better Tolerability***
DTG shows improved tolerability versus current preferred regimens with substantial reductions in treatment-limiting adverse drug reactions. Specifically, patients can avoid some of the psychiatric adverse events of EFV (ie depression and suicidal tendencies). Overall, general

patient feedback supports DTG as a highly tolerated medicine that is less likely to result in treatment discontinuation.

d. Higher genetic barrier to resistance

The higher genetic barrier of DTG means patients are less likely to develop resistance and therefore prolonging the need for second line treatment

WHEN TO USE ALTERNATIVE FIRST LINE REGIMENS

- When to use TDF+3TC+EFV
- Adults and adolescents aged 10 years and above should only be initiated on TDF+3TC+EFV if they are ineligible for DTG i. e.
  a. Women and adolescent girls of child bearing potential that intend to become pregnant or are not on effective contraception
  b. Pregnant women
  c. If weight does not allow for use of the currently available DTG formulations (containing 50mg)
  d. Diabetic patients on metformin if close laboratory monitoring is limited

When to use ABC+3TC+DTG

- Adults and adolescents eligible for DTG and aged 10 years and aboveshould only be initiated on ABC+3TC+DTG if TDF is contraindicated, including the following conditions:
- Kidney disease and estimated glomerular filtration rate (GFR) below 60 ml/min
- Adolescents below 35kg of weight.

RECOMMENDED FIRST-LINE REGIMEN FOR INITIATING ART IN PREGNANT OR BREASTFEEDING WOMEN

- PREFERRED FIRST-LINE REGIMEN: TDF+3TC+EFV
- All HIV-infected pregnant, and breastfeeding women should be initiated on tenofovir, lamivudine, and efavirenz (TDF+3TC+EFV)

When to use TDF+3TC+ATV/r

- Pregnant or breastfeeding women should only be initiated on TDF+3TC+ATV/r if EFV is contraindicated, including patients with history of psychosis.

Recommended first-line ARV regimen in adults, Adolescents, pregnant or breastfeeding women and children

PATIENT CATEGORY	PREFERRED REGIMEN	ALTERNATIVE REGIMEN
1. Adults and adolescents aged ≥10 years and ≥35kg		
1. 1. Adult men and adolescent boys 1. 2. Adult women and adolescent girls on effective contraception 1. 3. Adult women and adolescent girls not of child bearing potential	TDF+3TC+DTG	If DTG is contraindicated 1: TDF+3TC+EFV If TDF is contraindicated2: ABC+3TC+DTG
1. 4. Adult women and adolescent girls of child bearing potential who are pregnant, intend to get pregnant or not on effective contraception3, 4	TDF+3TC+EFV	If EFV is contraindicated: TDF+3TC+ATVr If TDF is contraindicated2: ABC+3TC+EFV
2. Children aged 0-<10 years and <35kg		
2. 1. Children <3 months	ABC+3TC+LPV/r (syrup)	ABC+3TC+RAL
2. 2. Children ≥3 months to <3 years of	ABC+3TC+LPV/r	ABC+3TC+RAL

age	(pellets)	
2. 3. Children ≥3 years to <10 years old	ABC+3TC+LPV/r (tablets)	ABC+3TC+DTG or ABC+3TC+RAL
1. Contraindications for DTG • Patients taking anticonvulsants; Carbamazepine, Phenytoin, Phenobarbital. Both DTG and EFV are contraindicated in patients taking anticonvulsants, these patients should be given a Protease Inhibitor based regimen • Use DTG with caution if a patient is diabetic and taking Metformin		
Contraindications for TDF • Renal disease and/or GFR <60ml/min • Weight<35kg 3. Women of childbearing potential not on contraceptives should be given information and counseled about the potential benefits and risks of DTG, including the risk of potential birth defects to allow for an informed decision on their ART regimen and contraceptive choices. If they choose DTG, their choice should be clearly documented and endorsed by the patient, parent or legal guardian in writing. 4. Effective contraception implies consistent use of duo-contraception with hormonal contraceptives + Condoms, tubo-ligation, vasectomy, implants and IUDs. 5. Substitute children on ABC+3TC+LPVr (syrup) to ABC/3TC/LPVr (pellets) at 3 months of age and to tablets at 3 years of age.		

First line ART

- Tenofovir + Lamivudine + Efavirenz one tablet a day (HS)

New drug INSTI (Integrase strand trans inhibitors)

- Dolutegravir + Lamivudine + Tenofovir once a day
- Undetectable viral load within 3 months
- Need dose adjustment if used together with Rifampicin
- Not to be taken with Calcium or Iron supplements or antacid
- Avoid in first 8-12 weeks of pregnancy
- If CD4 less than 200 cells/mm^3 need cotrimoxazole prophylaxis.
- If less than 100 be aware of cryptococcal meningitis
- Very low level of CD4 is associated with CMV.
- Herpes zoster can happen at any CD4 level but if lowCD4 can have repeated episodes and more extensive, if eye involved, blindness is a possible complication.
    - Treatment: Acyclovir 800mg 5 times/day 1 week – 10 days
- Usually, an ART regimen is to be chosen from first line ART regimens. TDF(Tenofovir) and 3 TC (Lamivudine) should be included, especially in the case of HBP coinfection.
- If there is a contraindication to TDF ie-GFR <50 ml/min, AZT (Zidovudine)+ 3 TC should be considered AZT should not be used if Hb is < 8 G/dl. For patients with advanced infection, who cannot be prescribed either TDF, because of increased creatinine and AZT, due to anaemia, ABC(Abacavir) + 3TC is an alternative.
- These 2 NRT must be combined with either EFV(NNRTI) or DTG (Dolutegravir, an integrase inhibitor).
- In clinically well males, postmenopausal females with little risk of TB IRIS, TDG is the drug of choice. Women of childbearing age should be a consistent contraception to be able to take DTG, as safety in the first trimester is still unknown. After 8 weeks of pregnancy and especially in pregnant women who present in the third trimester, DTG is the drug of choice because it rapidly suppresses viral load compared to other regimens.
- If TB IRIS (Immune Reconstitution Inflammatory Syndrome), develops while taking DTG, the regimen should not be changed to FEV. Instead, the dose is increased from 50 mg once to twice

daily, and reduced backed to once daily after completion of anti-TB. For those already on anti-TB drugs, FEV containing is the preferred one.

- The usual dose of FEV is 600mg once daily. The dose of daily FEV 600mg is associated with higher drug level in Asians- so EFV 400mg daily has been recently introduce, in Myanmar National Guidelines. But 400mg daily dose is not recommended to be used together rifampicin and during pregnancy- in which case the usual 600 mg dose should be used.
- The possible side effects of FEV include CNS side effects like dizziness, insomnia (which are seen in first weeks), depression and frank psychosis with self-harm (which are very rare), severe hepatitis (also very rare) and maculopapular rash (which is seldom severe).
- When switching ART regimens was limited in the past, patients were encouraged to continue the regimen by adding sedatives, antipsychotics and antihistamines, but in case of severe symptoms, the drug is stopped and changed to a PI/r (ritonavir boosted Protease Inhibitor) regimen. Now since DTG is available, it is suitable substitute to change if patients experience EFV side effects.
- EFV 400 mg is hoped to reduce these symptoms but FEV 400mg is for new initiation but rather, it is intended to replace FEV 600 mg being taken by many patients.
- DTG plasma level is reduced when taken together with polyvalent Cat ions(Mg, AL, Ca, Zn, Fe)So DTG should be taken 2 hours before or 6 hours after vitamins with minerals and cation containing antacids, laxatives and buffered medications.
- The general recommendation is to first treat the opportunistic infection(s) e.g., TB, PCP, cerebral toxoplasmosis or penicilliosis and start ART 2 weeks later. There are two other specific recommendations regarding the timing of ART initiation: the first is in patients with CD4 < 50 cells/mm3 and active TB. ART Should be started within 2 weeks of TB treatment initiation. Another is in patients with Cryptococcal meningitis, it is better to start ART 4- 6 weeks after the initiation of amphotericin infusion.
- The first few weeks and months after ART initiation usually requires more frequent follow-up visits. Drug hypersensitivity reactions (usually associated with FEV, Cotrim, Anti TB, if present are more commonly seen in the first few weeks) and unmasking or paradoxical IRIS (seen in in the first three months) are complications-if immediate attention is given, more serious consequences can be prevented.

Monitoring

- The expected CD4 improvement is approximately- a rise of 100-150 cells/mm3/year. If a person is started on ART with a very low CD4 count, ie. 100 cells/mm3 or less-immune reconstitution, in terms of rise in CD4 will take longer. In those whose baseline CD4 is higher, the response is more robust.
- Time to achieve an undetectable HIV viral load can take up to 24 weeks after starting ART. Regular viral load monitoring is more preferable than CD4 for assessing ART treatment response.
- The best monitoring tool for treatment success is viral load which is done at 6 – 12 months after ART and then annually.
- CD4 is monitored every 6 months, but in those with suppressed viral load(<1000 copies/ul) for one year it might not be necessary.
- Side effect monitoring is regimen-based: in a person taking TDF regular monitoring of serum creatinine, plasma potassium and urine RE is necessary
- For a person receiving Zidovudine containing ART, CBC needs to be checked regularly.

Success vs Failure of Treatment

- The goal of ART is to achieve and maintain an undetectable HIV viral load. On the other hand, if the viral load is more than 1000 copies/ul in a person who has been on ART for more than 6 months and this result is confirmed on a repeat test 2-3 months later, and non-adherence of ART can be ruled out, first line ART treatment failure can be defined. Switching of ART to second

line needs to be considered.

- The long –term success of treatment depends much on treatment adherence and regular follow-up. As there is still no cure yet for HIV lifelong ART is the only option.
- People on ART might have pill fatigue, emotional exhaustion in the need to visit regularly their health care provider and social economic factors that might have a negative effect on their treatment adherence. Health care workers need to be aware of the challenges they face- and be prepared to address them accordingly.
- In Myanmar there are more than 100 ART treatment centers in the public sector providing comprehensive care. HIV counselling, expert medical consultation, necessary diagnostic investigations and treatment support including ART can be assessed who are in need.
- Proper timely referral of those already diagnosed and those who need HIV testing is a duty of all health care providers.

MANAGING COMMON INFECTIONS AND COMORBIDITIES

- Most people with HIV die of opportunistic infections. Major opportunistic infection is need to be diagnosed and
- treatment started before starting ART. Giving ART without diagnosing and treating major
- Opportunistic infections in late disease will lead to disaster. However, in advanced states of immunosuppression typical signs and symptoms of infections will be absent or masked.
- It is important to be vigilant in treating late HIV. Unusual infections that do not occur in immunocompetent persons will also occur.

Prevention, screening and management of common co-infections

- The following are the major opportunistic infections seen in Myanmar:
  1. Mycobacterium tuberculosis
  2. *Pneumocystis jirovecii pneumonia*
  3. Toxoplasmosis
  4. Cryptococcosis
  5. Penicilliosis
  6. Histoplasmosis

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Definition

Autoimmune diseases sometimes appear after starting ART and this is known as autoimmune

- IRIS (thyrotoxicosis, SLE, sarcoidosis and other autoimmune disorders have been described
- after starting ART).
- IRIS usually starts within 2 to 3 months of starting ART but it may also be delayed for many
- months.
- IRIS is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to ART.
- It is a widely recognized phenomenon that occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after initiating therapy. IRIS should be considered only when the presentation cannot be explained by a new infection, the expected course of a known infection, or drug toxicity. The most serious and life-threatening forms of IRIS occur in patients co-infected with TB, Cryptococcus, Kaposi's sarcoma and herpes zoster

Risk factors for IRIS include:

- Very low CD4 count at start of ART
- Very high Viral Load and very rapid fall in Viral load after ART
- Short interval between OI treatment and ART
- Immediate ART initiation is not recommended in HIV infected patients with cryptococcal

meningitis due to the high risk of IRIS that may be life threatening IRIS. ART should not be started within first 1-2 weeks of Amphotericin initiation. It can be **started** within 2-5 weeks of induction and consolidation treatment with amphotericin B-containing regimens ***until there is evidence of a sustained clinical response to antifungal therapy.***

- When the underlying condition has no specific treatment however ART can be started immediately. Cryptosporidiosis, HIV associated dementia and progressive multifocal leukoencephalopathy are examples where ART is indicated immediately.

Differential diagnosis of IRIS includes

- Treatment failure of the OI (e.g. MDR TB)
- Adverse drug reaction
- A new OI (which is unmasking IRIS)

Treatment

The excessive inflammatory response ***is controlled*** with NSAIDs or steroids if necessary, which are gradually tapered according to symptoms. It may be necessary to stop ART only very rarely in life-threatening IRIS.

Managing IRIS

- IRIS is generally self-limiting, and interruption of ART is rarely indicated. Treat any co-infections to reduce morbidity and symptoms.
- If the sympwtoms are protracted, reassure the patient to prevent discontinuation of, or poor adherence to ART.

Post- exposure prophylaxis for healthcare workers

- Healthcare workers whose activities involve contact with HIV –infected patients, or who may come in contact with blood or body fluid from HIV-positive patients in a health care or laboratory setting are at risk for occupational exposure to HIV.
- The risk of infection via percutaneous exposure is approximately 0. 3%.
- The risk of infection after mucous membrane exposure is about 0. 09%. Needlestick injuries are the most common type of occupational exposure.
- If PEP is indicated, it should be started within 1-2 hours of exposure.

Details of recommended regimens are:

Category	Drug regimen
Basic	Zidovudine 300mgbid+Lamivudine150mg bid for 28 days
Expanded	Basic regimen+Indinavir 800mg tid or Nelfinavir 750mg tid for 28 days

Post-exposure prophylaxis (PEP)

- Post-exposure Prophylaxis (PEP) is a short-term antiretroviral treatment to reduce the likelihood of HIV infection after all potential exposures. PEP should be provided for both occupational (e.g. within health sector) and non-occupational (e.g. condom break with high risk sexual partner) exposures.

Preferred recommendations for adults, adolescents and children are:

- Alignment with recommendations on ART regimens for different age groups
- Emphasis on simplification to support completion rates

- Full course prescription (28 days)
- Adherence support

When considering the eligibility for PEP, the best practice guidance is as follows;

- PEP should be offered, and initiated as early as possible, to all persons with a HIV exposure, and preferably within 72 hours.
- Assessing the eligibility for PEP should be based on the HIV status of the source whenever possible and may include consideration of background prevalence and local epidemiological patterns.

Exposures that may warrant PEP include:

- exposure to bodily fluids (e.g. blood, semen, cervico-vaginal secretions, breast milk, amniotic fluids, cerebrospinal fluids, etc.)
- through mucous membranes such as sexual exposure and splashes to eyes, nose or oral cavity through parenteral/percutaneous exposures

Exclusions for PEP would include:

- when the exposed individual is already HIV positive when the source is HIV negative exposure to the bodily fluids that do not pose significant risk, i.e. tears, non-bloodstained saliva, urine and sweat

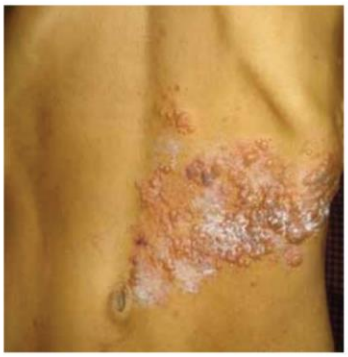
PEP provision and monitoring

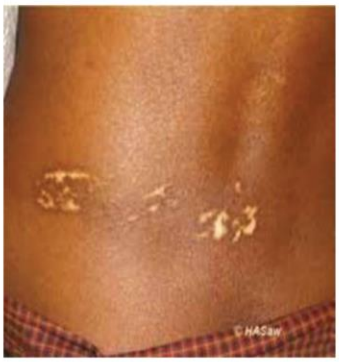
- A regimen for PEP for HIV with two ARV drugs is effective, but three drugs are preferred.
- PEP regimens for adults and adolescents:
    - TDF + 3TC (or FTC) is the preferred backbone.
    - LPV/r or ATV/r is the preferred third drug.
    - EFV is the alternative third drug.
- PEP regimens for children <10 years:
    - AZT+3TC is the preferred backbone.
    - ABC+3TC or TDF+3TC can be considered as alternatives.
    - LPV/r is the preferred third drugs.
- An age-appropriate alternative third drug can be identified among ATV/r, RAL, DRV, EFV and NVP.
- ***A 28 days prescription of antiretroviral drugs should be provided for PEP following initial risk assessment.***
- Timing of HIV testing in PEP: Baseline testing at day 0 (at the day of exposure) and follow-up testing is to be done at 3 and 6 month if day 0 is negative. If the exposed person is infected with Hepatitis C, window period may be prolonged. So follow up period may be prolonged up to one year.
- Enhanced adherence counselling is recommended for individuals initiating HIV PEP.

Prophylaxis for Maternal Transmission of HIV

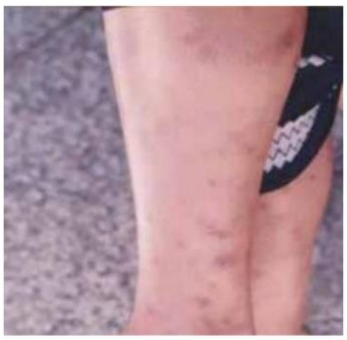
- The risk of vertical transnmission of HIV from mother to baby ranges from 7% to 40% Maternal HIV transmission is the primary means by which infants become infected. Hence prevention of maternal HIV transmission is of paramnount importance. Maternal HIV transmission can occur in utreo, during labour and delivery, or after birth(via breast-feeding). About 50-70% of maternalHIV transmission occurs in late pregnancy or during labour and delivery.
- Prophylactic therapy with antiretrovirals for mother and baby is recommended to prevent maternal transmission of HIV. Use OF FORmular feeding for the infants reduces the risk of transmission via breast-feeding.

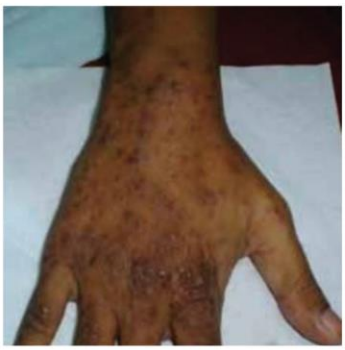
- Both Zidovudine and Nevirapine(administered as monotherapy for varying periods of time) have effective in reducing risk of maternal transmission.
- Nevirapine 200mg orally at onset of labour and 2mg/kg to babies within 72 hours of birth. This simple single- dose- to- mothe and single- dose-to-baby regimenof Nevirapine reduced maternal transmission.



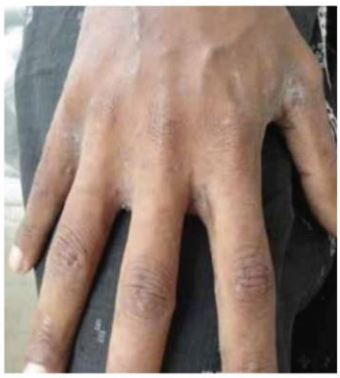


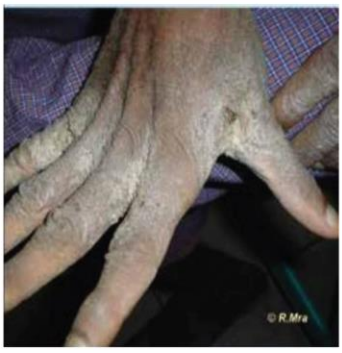
Herpes Zooster infection in Immunocompromised patients



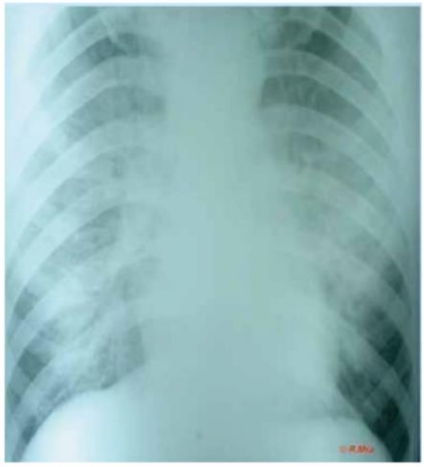


Pruritus Papular Nodules in immunocomprosied

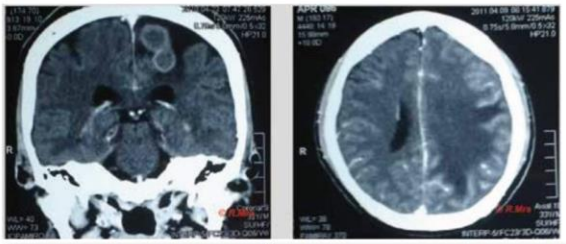




Crusted scabies or Norwegian scabies in immunocomprosied patients

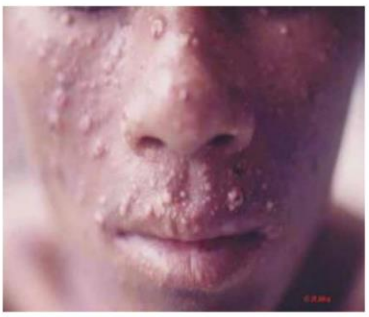


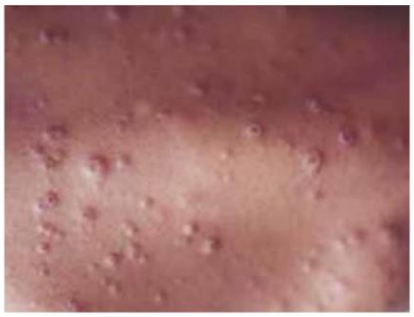
X-ray showed diffuse pulmonary infiltrates fanning out from the hilar region and sparing the apices and lower regions (Pneumocystis Pneumonia)

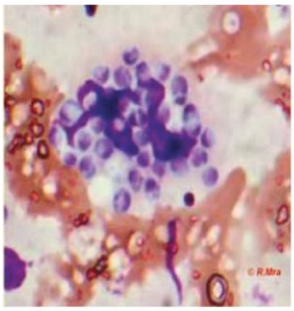


CT brain showing cerebral toxoplasmosis with multiple abscesses

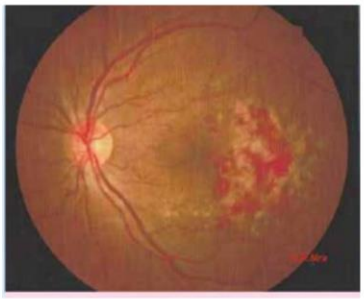
CT brain showing cerebral toxoplasmosis with massive cerebral edema



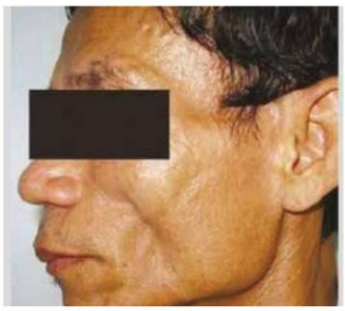




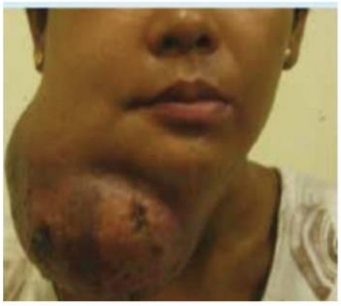
Penicilliosis on face(Umbilicated popular eruption and Fungal bodies are seen inside macrophages with a characteristic central septation with Leshman's or Giemsa stain



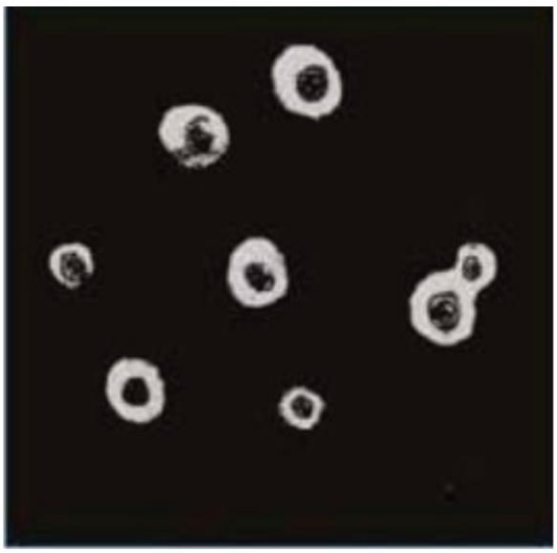
CMV Retinitis showing haemorrhagic necrosis of the retina with exudates



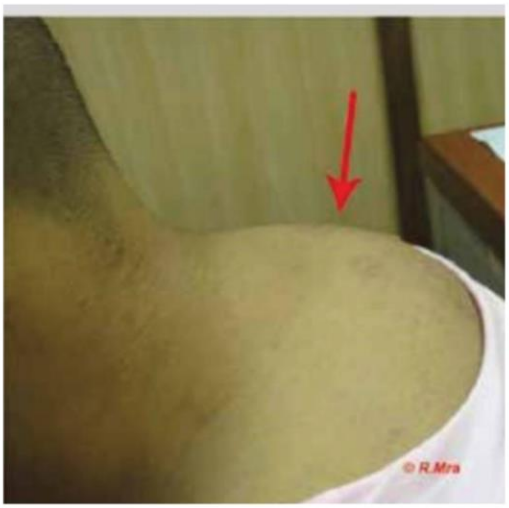
Lipoatrophy in HIV patient with long term treated with Stavudine



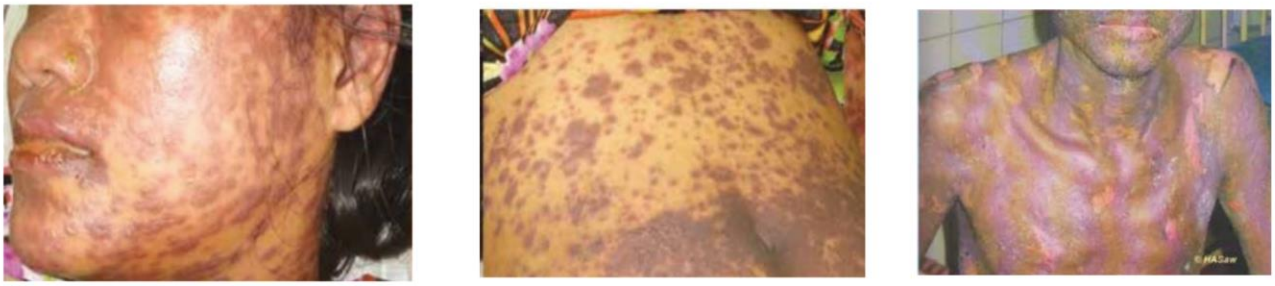
HIV associated Lymphoma



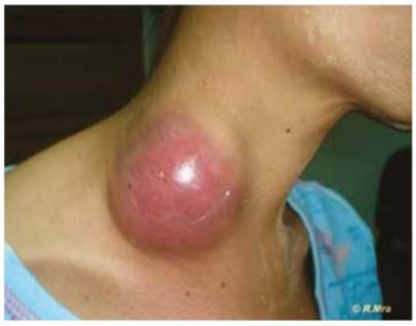
Yeast cells of Cryptococcus neoformans in India ink preparation (Sketch)



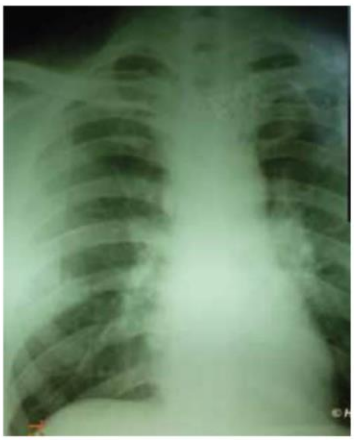
Lipo-hypertrophy in dorso-cervical region or buffalo hump appearance due to stavudine therapy



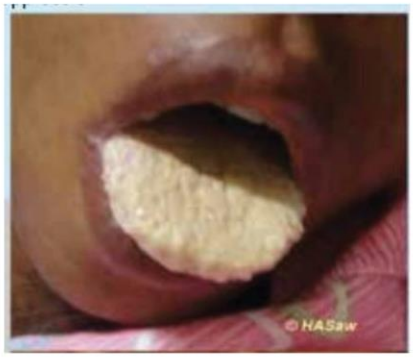
Stevens-Johnson syndrome due to nevirapine involving the whole body as well as mucus membrane (Right)and Toxic epiderma necrolysis (Left)

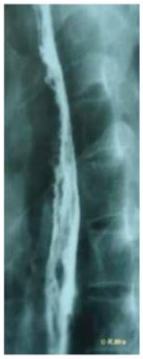


Immune Reconstitution Inflammatory Syndrome or IRIS



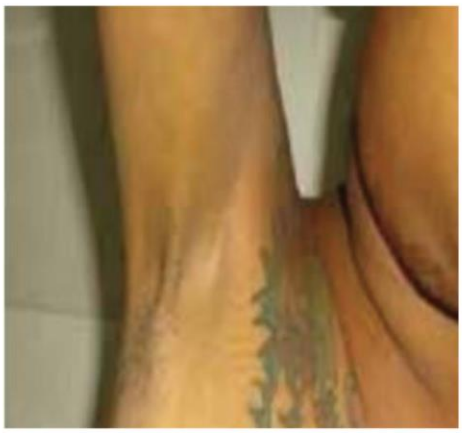
CXR showing hilar lymphadenopathy in HIV/AIDS patient

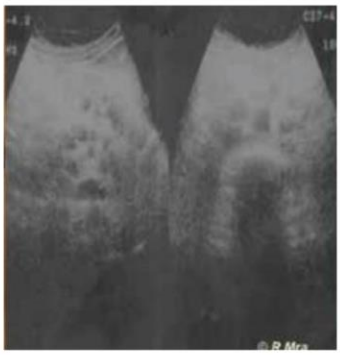


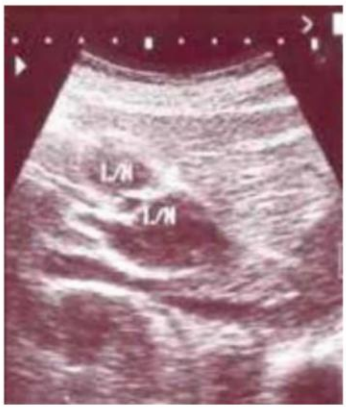


Oral Thrush in immunocompromised patients

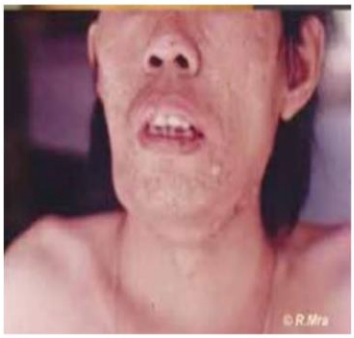
Oesophageal thrush with mucosal ulceration in Barium swallow



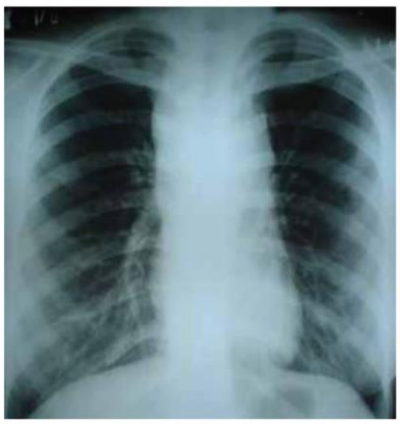




Intra-abdominal Lymphadenopathy in immunocompromised patients



Lymphadenopathy in HIV/TB patient



Mediastinal Lymphadenopathy and hilar lymphadenopathy in HIV/AIDS patient

TUBERCULOSIS

- Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. Until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS.
- **Pulmonary TB** is the most common form of the disease. Pulmonary TB is the form of TB which can be infectious and is responsible for transmission of infection in the community.
- **Extra pulmonary TB** affects organs other the lungs, most commonly pleura, lymphnodes, spine, joints, genitourinary tract, the nervous system and abdomen. TB may affect any part of the body.

TRANSMISSION OF TB

- A patient with pulmonary TB expels droplets of sputum containing tubercle bacilli into the air when coughing, laughing, or sneezing. These droplets remain suspended in the air for several hours and if a person inhales these particles, he may contract TB bacilli resulting in tuberculosis infection.

IDENTIFICATION OF PRESUMPTIVE TB

- A presumptive TB is any person who presents with symptoms and signs suggestive of TB, in particular with **cough for more than 2 weeks.** Cough is the most common symptom of pulmonary TB and present in 95% of all sputum smear positive TB cases.
- Other TB symptoms include:
    - Sputum expectoration
    - Haemoptysis
    - Chest pain
    - Fever
    - Breathlessness
    - Weight loss, loss of appetite
    - Night sweating
    - Lethargy

TB CASE Can be classified as the following.

- Bacteriological Result
- Drug resistance pattern
- Anatomical site of the disease
- History of previous treatment
- HIV status of patient

Bacteriological Result

- **A** bacteriologically confirmed TB case:
    - A biological specimen is positive by smear microscopy, culture or Gene X'pert.
    - Bacteriologically sensitive/susceptible TB
    - Bacteriologically resistant TB

A clinically diagnosed TB case:

- Bacteriologically not confirmed but diagnosed as TB by Radiology, Histology, Clinical and decided to treat by the experience Medical officer.

Drug Resistance Pattern

- Drug Susceptible TB (DSTB) - TB bacteria is susceptible to first line anti TB drugs

- Drug Resistant TB (DR TB)
    - MDR TB – resistant to Rifampicin and INH
    - Mono Resistant TB – resistant to one of antiTB drug
    - Poly resistant TB – res; to more than one antiTB drugs
    - Extensive Drug resistance TB (XDR TB) - MDR + additional resistant to Quinolone and Group A drugs
    - Totally Drug Resistance TB (TDR- TB)- Resistance to all anti TB drugs

Site of the Disease

- Pulmonary TB (PTB): bacteriologically confirmed or clinically diagnosed TB involved in the lung parenchyma or tracheobronchial tree.
- Extra-pulmonary TB (EPTB): bacteriologically confirmed or clinically diagnosed TB involved any organs other than the Lungs.

History of Previous Treatment

- New patient: No or <1 month Rx.
- Previously treated patient: >1 month Rx.
    - Relapse
    - Treatment after failure
    - Treatment after loss to follow up
    - Other previously treated patient
    - Patient with unknown Rx history

HIV Status of Patient

- HIV positive TB patient: HIV test + at the time of diagnosis or previous documented evidence.
- HIV negative TB patient: Negative result of HIV test at the time of TB diagnosis.
- HIV status unknown TB patient: No result of HIV test and no documented evidence for HIV.

DIAGNOSIS OF PULMONARY TUBERCULOSIS

- Sputum examination

Direct Sputum microscopy

- It is an appropriate technology and simple, specific, cheap, reliable and with rapid result.
- Two sputum samples are required as one early morning (Home collection) and one spot collection.

Sputum culture and DST -MDRTB

- Culture is the gold standard for TB diagnosis and also for MDR TB diagnosis. Other test is LPA (Line Probe Assay)
- Sputum for Gene X'pert (GXP)-MDRTB
    - GXP is a newer PCR based molecular technology to detect Rifampicin resistance (RR) (MDR TB diagnosis).
- Although it can detect *M. tuberculosis*, it is not routinely used for TB diagnosis in our context.

Chest X-ray (Conventional CXR & Digital CXR)

- **HIV Counselling &Testing -(HCT)** should be done for all registered TB cases to check HIV serological status of all TB patients and also need to refer the TB patients to NAP or NGO/INGO center properly for further management (TB/HIV collaborative activities) if

HIV positive.

- **Diabetes Mellitus (DM)** should be screened for TB patients to check gylcemic status of TB patients especially age over 40 years as TB/DM is becoming a common co morbidity.

RECOMMENDED TREATMENT REGIMENS FOR DIFFERENT TYPES OF TB PATIENTS

Treatment Category	Types of TB patient	Treatment course	
		Initial Intensive Phase	Continuation Phase
Initial treatment Regimen (IR)	**New,** **>15 yrs,** **bacteriologically confirmed or clinically diagnosed,** **HIV seropositive or not** Pulmonary Extra pulmonary	**2HRZE**	**4HR**
Retreatment Regimen (RR)	**Previously treated,** **bacteriologically confirmed or clinically diagnosed,** **HIV sero-positive or not:** Relapse Treatment after loss to follow-up Treatment after failure Other previously treated Unknown previous history	**3HRZE** **5HRE** **(OR)** **6HRZE***	

MONITORING TB PATIENTS

- Monitoring TB patients is to ensure that TB patient is responding to the treatment, and to decide the treatment outcome.
    - Sputum Follow up Examination
    - Body Weight
    - CXR

Treatment Category	Timing for Sputum Specimen
New Sputum Smear (+)ve PTB cases	2,5,6
Previously Treated PTB cases	3,5,8
New Sputum Smear Negative PTB/ EPTB Case	2,6

- In case of GXP referral, if RR is seen, GPs need to refer respective NTP centers for further confirmation and MDR TB management.

CRITERIA FOR GENE X'PERT TESTING

- All Pulmonary TB Cases (New/ Retreatment)
- Sputum Smear Positive at the end of the intensive Phase (Non- Converter)
- TB Patients with Diabetes Mellitus (TB/DM)
- Presumptive TB Cases (PLHIV/ Contacts with MDR-TB Patients)
- Other Cases to be considered individually by MDR-TB committee
- Any CXR abnormalities suggestive of TB (2022)

- In Yangon Region:
  - All Registered TB Cases are eligible for GXP testing.
  - There are GXP machines in all of State/Regions and District TB centers and some townships in Myanmar. ***If GXP is not available in the respective townships, GPs can refer the patients to nearest NTP centres where GXP is available.***
  - Types of specimen for GXP
    - Sputum
    - CSF
    - Gastric aspirate
    - Lymph node aspirate
  - Quality of Sputum for GXP testing
    - 2 early morning sputum samples
    - Mucopurulent sputum, not saliva
    - at least 2 ml
    - Not containing blood and particles
  - Don't leave the sample at 35°C for more than 3 days (Stable 4-10 days at 4°C)
  - Specimens should be held at 2-8°C during transportation

MDR TB TREATMENT

Standardized MDR-TB regimens used in Myanmar (Duration: 20 months)
6 (Amk Z Lfx Eto Cs) / 14 (Lfx Eto Cs Z) *(Amk = Amikacin, Z = Pyrazinamide, Lfx = Levofloxacin, Eto = Ethionamide, Cs = Cycloserine)*
PAS / Clofazimine will be added to the Standard MDR-TB Regimen in followings:
• Failures of retreatment regimen • Resistant to ofloxacin • The presence of the inhA gene on LPA (because ethionamide may not be effective) • The patient has a history of second-line drug use • The patient is a contact of a patient who died on second line drug regimen or a contact of a patient with a known history of resistance to second-line drugs

Update on DR TB Treatment

- DR-TB treatment regimens as per the National DR-TB guidelines (updates) (2022)
- ***OSSTR (9-12 months):***
  - 4-6 Bdq (6), Eto, Lfx, Cfz, Z, Hh, E/5 Lfx, Cfz, Z, E (Oral Shorter Tx Regimen)
- ***OLTR (18 months):***
  - 6 Bdq-Lfx- Lzd-Cfz/ 12 Lfx-Lzd-Cfz (Oral Longer Tx Regimen)
- ***Oral Shorter Pre XDR/XDR TB Treatment (Bpal) 6-9 months*** (Under operational research)
- Bedaquiline, Linezolid, Pretomanid-Duration
  - BPaLM: 6-9 Months: Bdq,Pa, Lzd, Mfx, (Lzd 600 mg daily)
- The 9-month, all-oral, bedaquiline-containing regimens are preferred over the longer (>18 months) regimen in adults and children with MDR/RR-TB, without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and with no extensive pulmonary TB disease or severe extrapulmonary TB.
- In these regimens, 2 months of linezolid (600 mg) can be used as an alternative to 4 months of ethionamide. Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on one of these regimens.
- Patients with extensive forms of DR-TB (e.g. XDR-TB) or those who are not eligible for or have failed shorter treatment regimens will benefit from an individualized longer regimen designed using the priority grouping of medicines recommended in current WHO guidelines.
- The 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid (600 mg) and

moxifloxacin, may be used programmatically in place of 9-month or longer (>18 months) regimens, in patients (aged ≥15 years) with MDR/RR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure).

- This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB). Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.

CHILDHOOD TB

- Risk Factors for Developing Childhood Tuberculosis
  - Close contact (household, close relatives, caregiver, neighbour and teacher) with a newly diagnosed smear-positive case as well as smear-negative but culture-positive case
  - Age <5 years of age
  - HIV infection
  - Severe malnutrition, measles and immunosuppressive drugs or illnesses
  - Absence of BCG vaccination
  - Failure to thrive or weight loss (documented)

Criteria for suspecting TB in Children

- The child can be considered as presumptive TB Case if 2 out 3 following features are present.
  - Persistence symptoms: cough for more than 2 week or fever (38 C) for more than 2 week
  - Failure to gain weight or weight loss (consult weight chart)
  - History of contact with suspected or diagnosed TB patient
- Symptoms suggestive of childhood TB include:
  - Cough for more than 2 weeks which is not improving with full course of appropriate antibiotics and/or bronchodilators
  - Fever (38°C) for more than 2 weeks after exclusion of common causes of fever (e.g. malaria)
  - Failure to gain weight (Weight loss if known) See weight chart Unexplained loss of appetite or lethargy

Signs suggestive of childhood TB are:

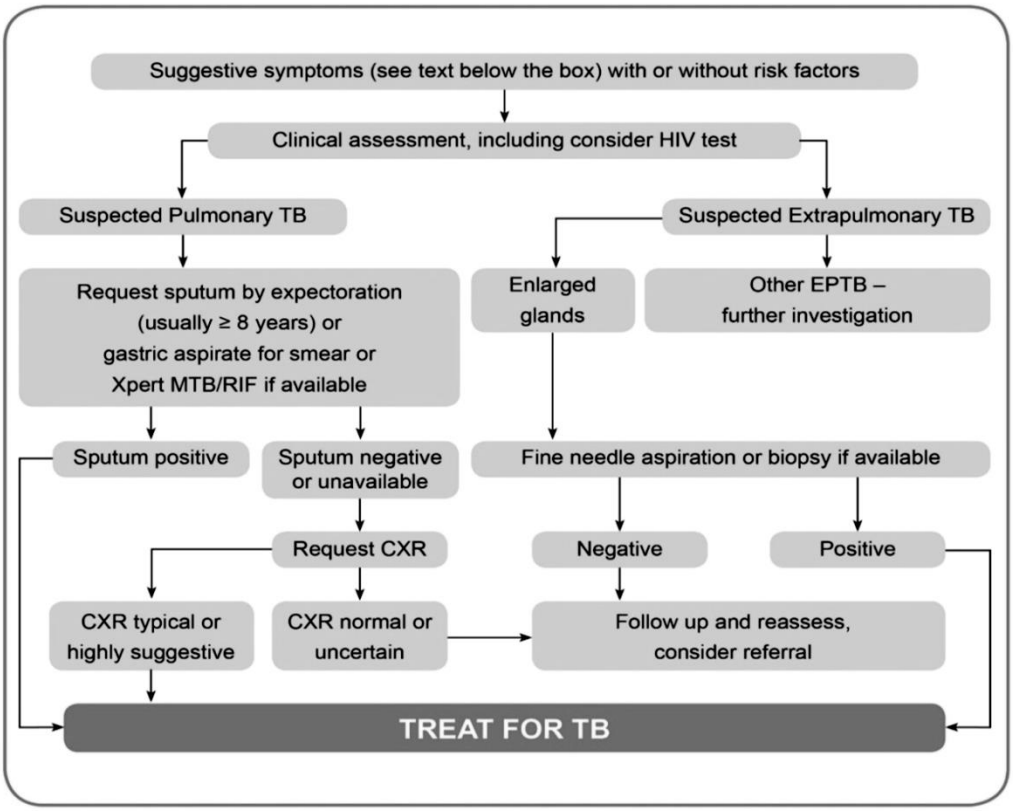
Pulmonary TB

- signs of persistent pneumonia (cough or difficulty breathing with fast breathing or chest indrawing) after full course of appropriate antibiotics

Extrapulmonary TB:

- Highly suggestive
  - Pleural effusion
  - Acute vertebral gibbus
  - Non-painful glands with fistula formation and/or draining sinus
- Suggestive
  - Meningitis not responding to adequate antibiotics
  - Pericardial effusion
  - Swollen non-painful joints
  - Significant enlarged lymph glands more than 2 cm in diameter and more than 2 in number without fistula formation but with no known local cause and not responding to usual antibiotics
  - Distended abdomen with Ascites
  - Clinical features indicative of tuberculin hypersensitivity (Erythema Nodosum, Phlyctenular conjunctivitis)

General Approach to diagnosis of TB in children



Criteria for suspecting TB in Children

The child can be considered as a presumptive TB case if 2 out of 3 following features are present.

- persistent symptoms: cough for more than 2 weeks and/or fever (≥38°C) for more than 2 weeks (unexplained)
- failure to gain weight or weight loss (consult weight chart)
- history of contact with presumptive or diagnosed TB patient

CHILDHOOD TB TREATMENT

	Type of TB patients	TB cases	Regimen	
			Intensive phase	Continuation phase
Recommended treatment regimens for children in each TB diagnostic categories	New cases	Children <8 years of age (exception: see below)	2HRZ	4HR
		• Children ≥8 years of age • Children <8years of age with severe form of pulmonary/ extrapulmonary TB or who are HIV-infected	2HRZE	4HR
		• Meningitis/disseminated TB • Osteoarticular TB	2HRZE	10HR
	Previously	• Relapse	3HRZE	5HRE

	treated case	• Treatment after failure • Treatment after loss of follow-up		
	MDRTB		Specially designed standardized or individualized regimens (refer to Chapter 5 and Myanmar National guidelines on Management of MDR-TB	

INFECTIVE CONTROL MEASURES AT GP CLINICS

- As a health care provider, every GPs need to be aware of, and careful about TB infection control measures at their daily GP settings for themselves, clinic staff and other attendants at the GP clinics. Key points for TB infection control measures for health care providers are as follows;

Administrative control measures

- To reduce the chances of exposure to airborne droplet nuclei (It is also most important and least expensive mean to health care personals)
- Triage (Fast track service) - Promptly identify persons with symptoms suggestive of TB
- Separate or isolate potentially infectious patients
- Control the spread of pathogens (cough etiquette)
- Minimize time spent in healthcare facilities by persons with symptoms suggestive ofTB
- Provide a package of HIV and TB care and prevention, that may include TB screening for staff

Environmental control measures

- reduce the concentration of airborne droplet nuclei
- Natural ventilation: simplest and least expensive technique by maximizing natural ventilation through open windows and doors.
    - Natural ventilation relies on open doors and windows, and permanent openings to bring in air from the outside.
    - When fresh air enters a room it dilutes the concentration of air particles inside the room, such as droplet nuclei containing *M tuberculosis*.
    - Designing rooms with adequate windows to maximize natural ventilation, can help reduce the spread of TB.
    - A rule of thumb is openable window area of 20%, preferably at opposite walls.
- **Mechanical ventilation:** more complex and costly methods.
    - AIIR (Airborne Infection Isolation Room)
    - Mechanical ventilation measures include electrical and wind-driven fans which may assist to
        i. distribute the air (thus allowing better dilution of air)
        ii. evacuate the air (fans pulling air out of a
        iii. maintain negative pressure ventilation systems (to ensure that air is pulled from adjacent rooms into the negative pressure patient room).

Personal protective equipment

- **To** protects HCWs from inhaling infectious droplet nuclei
    - Surgical Masks
        - Reduce spread of Micro-organisms from wearer
        - Not provide protection to the wearer from inhaling small infectious aerosols.
        - Uses for **PATIENT** (not for staff)

- Respirators - N95/FFP2 for **Health Care Worker** (HCW) and non infected person

Health Education and Counselling

- Health Education and Counselling plays a crucial role for every TB patients, family and caregivers.
- GPs need to do HE& Counselling about TB mainly relating to the adherence to anti TB treatment, side effects of anti TB drugs, TB transmission and prevention, proper nutrition, follow up sputum examination, TB infection control etc...

TB PREVENTIVE THERAPY (TPT)

- The main health care intervention available to reduce the risk of TB infection progressing to active TB disease is TB preventive treatment. Other interventions are TB infection prevention and control, and vaccination of children with the bacille Calmette-Guérin (BCG) vaccine, which can confer protection, especially from severe forms of TB in children.
- WHO guidance recommends TB preventive treatment for people living with HIV, household contacts of bacteriologically confirmed pulmonary TB cases and clinical risk groups (e.g. those receiving dialysis)
- It is estimated that a quarter of the world population is infected with TB
- 5-10% of those will develop TB in their lifetime
- Most of those develop TB within 5 years since the infection
- With the current available LTBI treatment, the risk to progress from infection to active disease can be reduced 60-90%

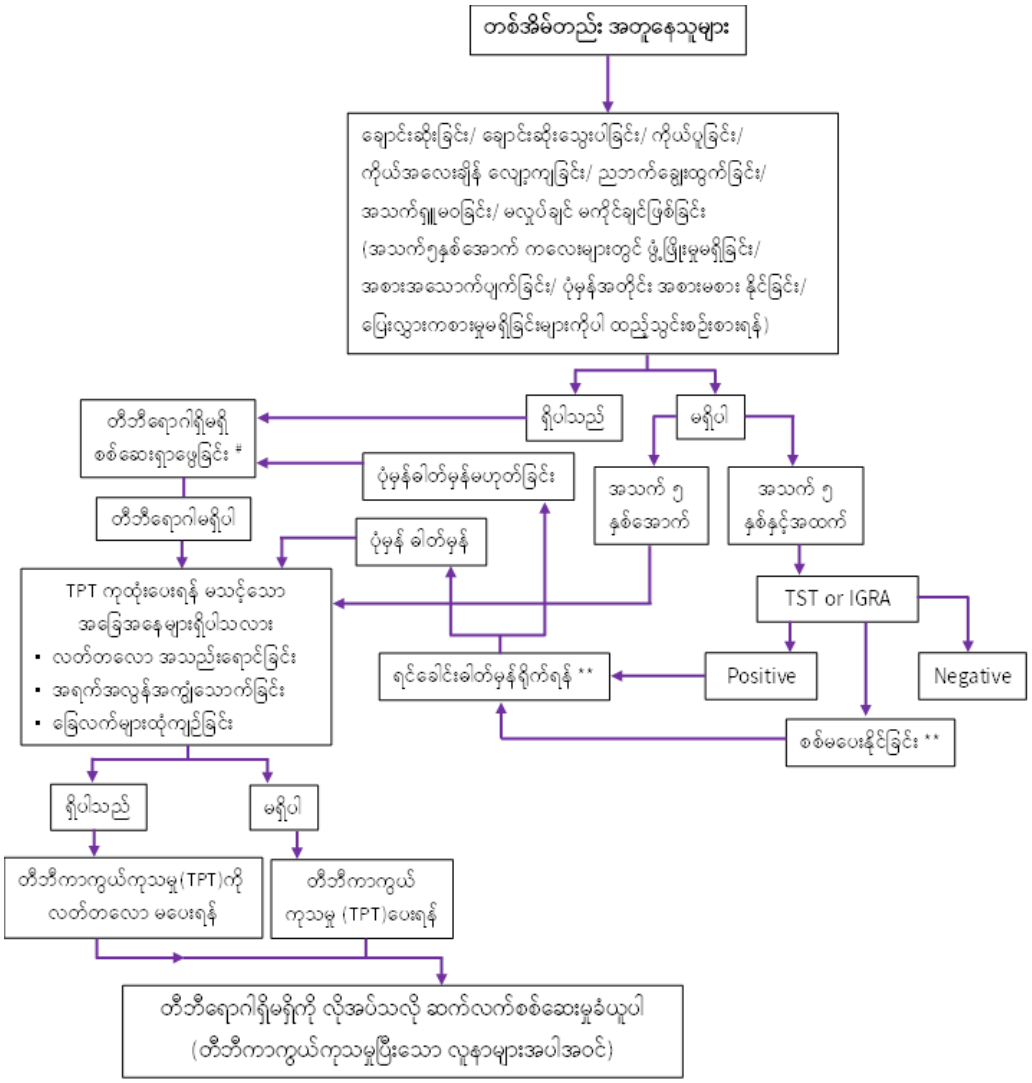
LATENT TUBERCULOSIS INFECTION (LTBI):

- A state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB.

Diagnosis

- Two approved testing:
    i. Tuberculin skin test (TST)
    ii. Interferon γ release assay (IGRA), ex: TSPOT®TB Test, QuantiFERON®TB Gold in Tube Test)
- The tests measure the immune response against MTB, not the presence of MTB itself
- Neither TST nor IGRAs can distinguish LTBI from active TB and past TB
- Adjunct tests where diagnosis of TB is uncertain.

Algorithm for Initiation TPT in Myanmar



WHO recommended Treatment Options for LTBI

စဉ်	ကုထုံး	အတို ကောက်	အကြိမ်ရေ	ကိုယ်အလေးချိန်အရ သုံးရမည့် ဆေးပမာဏ	အများဆုံး သောက်ရမည့် ဆေးပမာဏ
၁။	INH ဖြေ	6H	နေ့စဉ် (၁) ကြိမ် (180 doses)	အသက်(၂)နှစ်အထိ - 10mg/kg/day (range, 7-15 mg/kg)	300 mg
၂။	Rifapentine နှင့် high dose Isoniazid ဥလ	3HP	အပတ်စဉ် (၁) ကြိမ် (12 doses)	အောက်ဖော်ပြပါဇယားအတိုင်း တွက်ချက်ပေးရမည်။	INH - 900mg Rifapentine - 900 mg

အသက် ၂ နှစ်မှ ၁၄နှစ် အထိ

Formulation	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg
INH 100 mg	3	5	6	7	7
Rifapentine 150 mg	2	3	4	5	5
INH + rifapentine FDC (150 mg/ 150 mg)	2	3	4	5	5

အသက် ၁၄နှစ်အထက်

Formulation	30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70kg
INH 300 mg	3	3	3	3	3
Rifapentine 150 mg	6	6	6	6	6
INH + rifapentine FDC (300 mg/ 300 mg)	3	3	3	3	3

REFERENCES

1. *Training manual on PPM TB for GPs (2020): NTPIWHOIMMA*
2. *Global TB Report, WHO (2021):*
3. *Guidelines for treatment of drug-susceptible TB in Myanmar (2020)*
4. *Update information from National TB Program/WHO (2021)*

MALARIA

DEFINITION:

- Malaria is a parasitic disease transmitted by bite of infected female Anopheles mosquitoes that bite at night.
- Human malaria parasites:
  - *Plasmodium falciparum* - most common (around 60%), and causes severe diseases.
  - *Plasmodium vivax*- around 40%, and rarely causes severe diseases.
  - Others are *Pl. ovale, Pl. malariae*

SUSPECTED MALARIA

- A person with fever within 7 days with or without other accompanying signs and symptoms, has either history of malaria or had stayed at night in areas where there is malaria transmission and has no obvious signs and symptoms of any other febrile disease.

PROBABLE MALARIA

- Test (either by microscopy and/or rapid diagnostic test) and is treated with full course of antimalaria drugs.

CONFIRMED MALARIA

- A case of febrile illness or asymptomic, infected with malaria parasites confirmed by either microscopy and /or rapid diagnostic test (RDT)

UNCOMPLICATED MALARIA

- Symptomatic malaria parasitaemia with no signs of severity and/ or evidence of vital organ dysfunction.

SEVERE FALCIPARUM MALARIA

- Acute falciparum malaria with signs of severity and/or evidence of vital organ dysfunction or malaria with pregnancy.

UNCOMPLICATED MALARIA

- A person living in malaria endemic area or history of travel to malaria area within past 6 weeks with onset of fever and one or more of the followings.
- Malaria attack (6-l0hr)

CLINICAL FEATURES
Symptoms

- Sensation of cold, shivering
- Intermittent fever
- headaches
- vomiting
- seizures in young children

- Sweats return to normal temperature
- Tiredness

Signs

- Temperature above 38° C
- Splenomegaly
- Pallor
- No other obvious signs of febrile diseases

DIAGNOSIS

- Microscopy with Giemsa stained thick and thin blood film (gold standard)
- RDT
- Immunochromatographic test for malaria antigen. Can detect malaria antigens in 15 minutes
- Positive as soon as the parasites present in the blood.
- RDTs to detect pLDH *(pan-Plasmodium* antigen lactate dehydrogenase) may remain positive up to *5-6 days after disappearance* of parasites, while those to detect HRP2 (Histidine rich protein 2) remain positive up *to 2-3 weeks after disappearance* of parasites. /-found in infected RBC or as free antigens in serum or plasma

Helpful in diagnosis of acute infection

- **Rapid Immunodiagnostic Strip Tests** Simple and rapid device tests Reliable; detects *Pf* alone or *P.f/P.v*
- RDT is interestingly used where microscopy is not feasible or quality of malaria microscopy result is not promising.

TREATMENT OF UNCOMPLICATED P. FALCIPARUM MALARIA

- ARTEMETHER-LUMEFANTRINE (20 mg/120 mg) (dosage 1.5/12mg/kg BD +
- primaquine 0.25mg/kg)
- DIHYDROARTEMISININ-PIPERAQUINE (40 mg/320 mg) (dosage 96.4 mg and
- 51.2mg/kg)
- ARTESUNATE -MEFLOQUINE

Treatment regime of P. falciparum malaria

Age group (Years)	Artemether-Lumefantrine + Primaquine						
	Day 0		Day1		Day2		
	AL 1st Dose	AL 2nd Dose	AL 1st Dose	AL 2nd Dose	AL 1st Dose	PQ (Stat)	AL 2nd Dose
<1	½	½	½	½	½	0	½
1 – 4	1	1	1	1	1	7.5mg	1
5 – 9	2	2	2	2	2	15mg	2
10 – 14	3	3	3	3	3	30mg	3
15+above	4	4	4	4	4	45 mg	4

Day0: Day of blood Test & Positive; Day1: one day after blood test (+);
Day2: 2days after blood test(+)
This regime has been updated in 2020. Primaquine is given for gametocytocidal purpose to prevent onward transmission.

TREATMENT OF P. VIVAX, P. MALARIAE, P. OVALE

- Chloroquine (dosage 25 mg base/kg for 3 days) is still the treatment of choice for malaria
- Radical cure is achieved by primaquine (dosage 0.25 mg/kg/day for 14 days) should be given for confirmed *P. vivax* and *ovale* infections with precautions.
- If the patient is expected to has G6PD deficiency then O.75 mg/kg is given once weekly for 8 weeks.

Age group (years)	Dose of chloroquine tablets (150 mg base)		
	Day 1	Day2	Day3
< 1	1/3	1/3	1/3
1- 4	l½	l½	l½
5-9	2	2	2
10 -14	3	3	3
>15	4	4	4

- Primaquine (for *P. vivax*, *P. ovale* Hyponozoites)
- Daily regime - good compliance, more side effects
- Weekly regime - compliance not good, but less side effects

IMPORTANT MESSAGE FOR PATIENTS

- Stop taking PQ if there is blue coloration of lips, nails or changing urine color (red/dark urine) and come immediately to the health center.

TREATMENT IF PLASMODIUM MALARIAE

- Chloroquine (25mg/kg) within 3 days is effective.

TREATMENT OF MIXED INFECTIONS (P.F+ OTHER)

- Any of the above three ACTs recommended for treatment of uncomplicated *P. falciparum* malaria in Myanmar should be given, plus a full course of Primaquine as appropriate for *P.vivax* and/or *P. ovale* infections.

TREATMENT OF MALARIA IN PREGNANCY

- *First trimester:*
  - Quinine plus Clindamycin is to be given for 7 days
  - AL for 3 days is indicated only if this is the only treatment immediately available, or if treatment with 7-day Quinine plus Clindamycin fails or if there is uncertainty of compliance with a 7-day treatment of Quinine or Clindamycin.
- *Second and Third trimester:*
  - AL to be given for 3 days (no primaquine)
- *Lactating Women:*
  - The amounts of anti-malarial that enter breast milk and are consumed by the breastfeeding infant are relatively small.
  - Tetracycline is contraindicated in breastfeeding mothers because of its potential effect on the infant's bone and teeth. Primaquine should not be used in nursing women up to 6 months of lactating period, unless the breastfed infant has been determined not to be G6PD-deficient.
  - AL to be given for 3 days
  - Primaquine should not be given to breast feeding mothers of infants <6 months of age

SEVERE MALARIA

Definitions

- **Severe P. falciparum malaria**
- For epidemiological purposes**, severe falciparum** malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia.

CLINICAL FEATURES

- Altered or decreased consciousness (e.g. confusion, delirium, coma)
- Convulsions more than two episodes in 24 hrs
- Persistent vomiting (this may also be a neurological manifestation)
- Prostration, i.e. generalized weakness so that the patient is unable to walk or sit up without assistance
- Hyperpyrexia (39° C & higher, with dry skin)
- Severe anaemia
- Failure to pass urine or passing a very small quantity of urine/ renal failure
- Pulmonary oedema (difficulty in lying flat due to breathing problems usually with cough, pink frothy sputum)
- Circulatory collapse (shock) - shown by a feeble, very rapid pulse and cold and clammy limbs
- Spontaneous bleeding
- Haemoglobinuria (black urine)
- Jaundice, yellow coloration of the eyes, failure to respond to treatment within 3 to 7 days
- (first four categories are included in Non per-os patients)
- Malaria *(Pf+)* in Pregnancy

LABORATORY FINDINGS:

- Hypoglycaemia (blood glucose< 2.2 mmol/1 or <40 mg/dl)
- Metabolic acidosis (plasma bicarbonate <15 mmol/1)
- Severe normocytic anaemia (Hb < 5 g/dl, packed cell volume <15%)
- Haemoglobinuria
- Hyperparasitaemia (>2%/100 000/micro 1 in low intensity transmission areas or >5% or 250000/ micro 1 in areas of high stable malaria transmission intensity)
- Hyperlactataemia (lactate - > 5mmol/l)
- Renal impairment (serum creatinine >265 µmol/1)

SEVERE *P. VIVAX* AND *P. KNOWLESI* MALARIA

- Severe *P. vivax* malaria is defined as for falciparum malaria but with no parasite density thresholds.
- Severe *P. knowlesi* malaria is defined as for falciparum malaria but with two differences:
- *P. knowlesi* hyperparasitaemia: parasite density>100 000/µL
- Jaundice and parasite density > 20 000/ µL.

TREATMENT OF SEVERE AND COMPLICATED MALARIA

- Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular Artesunate for at least 24 hr and until they can tolerate oral medication
- Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy,

complete treatment with 3 days of an ACT (Artimisinin based combination therapy) (A+L) plus primaquine if not contraindicated.

PRE-REFERRAL TREATMENT BEFORE REFERRAL

- Severe malaria is ***a medical emergency.*** After rapid clinical assessment, full doses of an effective parenteral antimalarial medicine that is immediately available should be given without delay, even when/where confirmatory diagnosis is not immediately possible.
- The drug of choice is Artesunate given by the intravenous (IV) or intramuscular (IM) route.
- Other options if intravenous or intramuscular Artesunate is not available - Artemether (IM) or Quinine dihydrochloride should be used immediately.
- ****50% Glucose injection for life saving if hypoglycemia is suspected**** especially in patients treated with Quinine (Quinine induced hypoglycaemia)*
- Artesunate
- Recommended Dose 2.4 mg/kg stat, 2.4 mg/kg after 12 and 24 hrs and daily until the patient can tolerate oral medication

CHEMOPROPHYLASIX

- Generally, chemoprophylaxis is not recommended because of drug side effects, false security and also poor effectiveness.

Stand-by Curative Treatment

- For travelers to endemic areas (>10 days) where early access to diagnosis and effective treatment is not possible, stand -by curative treatment is recommended using RDT and recommended ACTs.
- Other measures to prevent mosquito bites should be promoted such as use of repellents and LLINs or ITNs.
- There is no intervention that provides 100% effectiveness in preventing malaria.

Preventive measures

- Malaria prevention can be done through
- Insecticide Treated Nets (ITNs) and Long Lasing Insecticide Treated Nets (LLINs)
- Sleeping inside mosquito nets treated with insecticides at night is a cost-effective mean for malaria prevention for indoor biter vectors. Mosquito bite can be avoided by applying mosquito repellents over the exposed parts of the body.
- Control of Malaria Vectors
- Early Diagnosis and Effective Treatment with recommended drugs (EDET)

REFERANCES

1. *Therapeutic Manual Internal Medicine (1st Edition ,2016)*
2. *Malaria Manual for Clinicians and Private General Practitioners (3rd Edition,2017)*
3. *WHO Guideline for the Treatment of Malaria, Third Edition*

SEXUALLY TRANSMITTED DISEASES

- The term “sexually transmitted infection” (STI) refers to a pathogen that causes infection through sexual contact, whereas the term “sexually transmitted disease” (STD) refers to a recognizable disease state that has developed from an infection.
- Sexually transmitted diseases (STDs) — or sexually transmitted infections (STIs) — are generally acquired by sexual contact. The bacteria, viruses or parasites that cause sexually transmitted diseases may pass from person to person in blood, semen, or vaginal and other bodily fluids.
- Sometimes these infections can be transmitted nonsexually, such as from mothers to their infants during pregnancy or childbirth, or through blood transfusions or shared needles.

What are the top 10 sexually transmitted diseases

- Genital shingles (Herpes Simplex)
- Human papillomavirus (Genital warts)
- Hepatitis B
- Chlamydia
- Chancroid (Syphilis)
- Clap (Gonorrhea)
- Human immunodeficiency virus/Acquired immunodeficiency syndrome (HIV/AIDS)
- Trichomoniasis (Trich)
- Bacterial vaginosis

Syndrome	**Symptoms**	**Signs**	**Most common causes**
Vaginal discharge	*Unusual vaginal discharge* *Vaginal itching* *Dysuria (pain on urination)* *Dyspareunia (pain during sexual intercourse)*	*Abnormal vaginal discharge*	*VAGINITIS:* *– Trichomoniasis* *– Candidiasis* *CERVICITIS:* *– Gonorrhoea* *– Chlamydia*
Urethral discharge	*Urethral discharge* *Dysuria* *Frequent urination*	*Urethral discharge (if necessary, ask patient to milk urethra)*	*Gonorrhoea* *Chlamydia*
Genital ulcer	*Genital sore*	*Genital ulcer*	*Syphilis* *Chancroid* *Genital herpes*
Lower abdominal pain	*Lower abdominal pain* *Dyspareunia*	*Vaginal discharge* *Lower abdominal tenderness on palpation* *Temperature >38°*	*Gonorrhoea* *Chlamydia* *Mixed anaerobes*
Scrotal swelling	*Scrotal pain and swelling*	*Scrotal swelling*	*Gonorrhoea* *Chlamydia*
Inguinal bubo	*Painful enlarged inguinal lymph nodes*	*Enlarged inguinal lymph nodes* *Fluctuation* *Abscesses or fistulae*	*LGV* *Chancroid*
Neonatal conjunctivitis	*Swollen eyelids* *Discharge* *Baby cannot open eyes*	*Oedema of the eyelids* *Purulent discharge*	*Gonorrhoea* *Chlamydia*

- STDs or STIs can have a range of signs and symptoms, including no symptoms. That's why they

may go unnoticed until complications occur or a partner is diagnosed.

- Signs and symptoms that might indicate an STI include:
- Sores or bumps on the genitals or in the oral or rectal area
- Painful or burning urination
- Discharge from the penis
- Unusual or odorous vaginal discharge
- Unusual vaginal bleeding
- Pain during sex
- Sore, swollen lymph nodes, particularly in the groin but sometimes more widespread
- Lower abdominal pain
- Fever
- Rash over the trunk, hands or feet
- Signs and symptoms may appear a few days after exposure. However, it may take years before you have any noticeable problems, depending on the organism causing the STI.

When to see a doctor

- See a doctor immediately if:
- You are sexually active and may have been exposed to an STI
- You have signs and symptoms of an STI
- Make an appointment with a doctor:
- When you're considering becoming sexually active or when you're 21 — whichever comes first
- Before you start having sex with a new partner

Sexually transmitted disease (STD) symptoms

- If you have sex — oral, anal or vaginal intercourse and genital touching — you can get an STD, also called a sexually transmitted infection (STI). Regardless of your marital status or sexual orientation, you're vulnerable to STIs and STI symptoms. Thinking or hoping your partner doesn't have an STI is no protection — you need to know for sure.
- Condoms, when properly used, are highly effective for reducing transmission of some STDs. But no method is foolproof, and STI symptoms aren't always obvious. If you think you have STI symptoms or have been exposed to an STI, see a doctor. Also, inform your partner or partners so that they can be evaluated and treated.
- Some STIs are easy to treat and cure; others require more-complicated treatment to manage them.
- If untreated, STIs can increase your risk of acquiring another STI such as HIV. This happens because an STI can stimulate an immune response in the genital area or cause sores, either of which might raise the risk of HIV tntreated STIs can also lead to infertility, organ damage, certain types of cancer or death.

Asymptomatic STIs

Many STIs have no signs or symptoms (asymptomatic). Even with no symptoms, however, you can pass the infection to your sex partners. So it's important to use protection, such as a condom, during sex. And visit your doctor regularly for STI screening so you can identify and treat an infection before you can pass it on.

Chlamydia symptoms

- Chlamydia is a bacterial infection of your genital tract. Chlamydia may be difficult to detect because early-stage infections often cause few or no signs and symptoms. When they do occur, symptoms usually start one to three weeks after you've been exposed to chlamydia and may be mild and pass quickly.
- Signs and symptoms may include:
- Painful urination
- Lower abdominal pain
- Vaginal discharge in women
- Discharge from the penis in men
- Pain during sexual intercourse in women
- Bleeding between periods in women
- Testicular pain in men

Gonorrhea symptoms

- Gonorrhea is a bacterial infection of your genital tract. The bacteria can also grow in your mouth, throat, eyes and anus. The first gonorrhea symptoms generally appear within 10 days after exposure. However, some people may be infected for months before signs or symptoms occur.
- Signs and symptoms of gonorrhea may include:
- Thick, cloudy or bloody discharge from the penis or vagina
- Pain or burning sensation when urinating
- Heavy menstrual bleeding or bleeding between periods
- Painful, swollen testicles
- Painful bowel movements
- Anal itching

Trichomoniasis symptoms

- Trichomoniasis is a common STI caused by a microscopic, one-celled parasite called Trichomonas vaginalis. This organism spreads during sexual intercourse with someone who already has the infection.
- The organism usually infects the urinary tract in men, but often causes no symptoms. Trichomoniasis typically infects the vagina in women. When trichomoniasis causes symptoms, they may appear within five to 28 days of exposure and range from mild irritation to severe inflammation.
- Signs and symptoms may include:
- Clear, white, greenish or yellowish vaginal discharge
- Discharge from the penis
- Strong vaginal odor
- Vaginal itching or irritation
- Itching or irritation inside the penis
- Pain during sexual intercourse
- Painful urination

HIV symptoms

- HIV is an infection with the human immunodeficiency virus. HIV interferes with your body's ability to fight off viruses, bacteria and fungi that cause illness, and it can lead to AIDS, a chronic, life-threatening disease.
- When first infected with HIV, you may have no symptoms. Some people develop a flu-like illness, usually two to six weeks after being infected. Still, the only way you know if you have HIV is to be tested.

Early signs and symptoms

- Early HIV signs and symptoms usually disappear within a week to a month and are often mistaken for those of another viral infection. During this period, you're highly infectious. More-persistent or -severe symptoms of HIV infection may not appear for 10 years or more after the initial infection. Early-stage HIV symptoms may include:
    - Fever
    - Headache
    - Sore throat
    - Swollen lymph glands
    - Rash
    - Fatigue
- As the virus continues to multiply and destroy immune cells, you may develop mild infections or chronic signs and symptoms such as:
    - Swollen lymph nodes — often one of the first signs of HIV infection
    - Diarrhea
    - Weight loss
    - Fever
    - Cough and shortness of breath
    - Late-stage HIV infection
- Signs and symptoms of late-stage HIV infection include:
    - Persistent, unexplained fatigue
    - Soaking night sweats
    - Shaking chills or fever higher than 100.4 F (38 C) for several weeks
    - Swelling of lymph nodes for more than three months
    - Chronic diarrhea
    - Persistent headaches
    - Unusual, opportunistic infections

Genital herpes symptoms

- Genital herpes is a highly contagious STI caused by a type of the herpes simplex virus (HSV) that enters your body through small breaks in your skin or mucous membranes. Most people with HSV never know they have it, because they have no signs or symptoms or the signs and symptoms are so mild they go unnoticed.
- When signs and symptoms are noticeable, the first episode is generally the worst. Some people never have a second episode. Others, however, can have recurrent episodes for decades.
- When present, genital herpes signs and symptoms may include:
    - Small red bumps, blisters (vesicles) or open sores (ulcers) in the genital and anal areas and areas nearby
    - Pain or itching around the genital area, buttocks and inner thighs
    - Ulcers can make urination painful. You may also have pain and tenderness in your genital area until the infection clears. During an initial episode, you may have flu-like signs and symptoms, such as a headache, muscle aches and fever, as well as swollen lymph nodes in your groin.
    - In some cases, the infection can be active and contagious even when sores aren't present.

Human papillomavirus (HPV) infection and genital warts symptoms

- HPV infection is one of the most common types of STIs. Some forms of HPV put women at high risk of cervical cancer. Other forms cause genital warts. HPV usually has no signs or symptoms.
- The signs and symptoms of genital warts include:
    - Small, flesh-colored or gray swellings in your genital area
    - Several warts close together that take on a cauliflower shape

    - Itching or discomfort in your genital area
    - Bleeding with intercourse
- Often, however, genital warts cause no symptoms. Genital warts may be as small as 1 millimeter in diameter or may multiply into large clusters. Warts can also develop in the mouth or throat of a person who has had oral sex with an infected person.

Hepatitis symptoms

- Hepatitis A, hepatitis B and hepatitis C are all contagious viral infections that affect your liver. Hepatitis B and C are the most serious of the three, but each can cause your liver to become inflamed.
- Some people never develop signs or symptoms. But for those who do, signs and symptoms may occur several weeks after exposure and may include:
    - Fatigue
    - Nausea and vomiting
    - Abdominal pain or discomfort, especially in the area of your liver on your right side beneath your lower ribs
    - Loss of appetite
    - Fever
    - Dark urine
    - Muscle or joint pain
    - Itching
    - Yellowing of your skin and the whites of your eyes (jaundice)

Syphilis symptoms

- Syphilis is a bacterial infection. The disease affects your genitals, skin and mucous membranes, but it can also involve many other parts of your body, including your brain and your heart.
- The signs and symptoms of syphilis may occur in three stages — primary, secondary, and tertiary. Some people also experience latent syphilis, in which blood tests are positive for the bacteria but no symptoms are present.
- At first, only a small, painless sore (chancre) may be present at the site of infection, usually the genitals, rectum, tongue or lips. As the disease worsens, symptoms may include:
    - Rash marked by red or reddish-brown, penny-sized sores over any area of your body, including your palms and soles
    - Fever
    - Enlarged lymph nodes
    - Fatigue and a vague feeling of discomfort
    - Soreness and aching
- Without treatment, syphilis bacteria may spread, leading to serious internal organ damage and death years after the original infection.
- Some of the signs and symptoms of late-stage syphilis include:
    - Lack of coordination
    - Numbness
    - Paralysis
    - Blindness
    - Dementia

  There's also a condition known as congenital syphilis, which occurs when a pregnant woman with syphilis passes the disease to her unborn infant. Congenital syphilis can be disabling, even life-threatening, so it's important for pregnant women with syphilis to be treated.

Neurosyphilis

- At any stage, syphilis can affect the nervous system. Neurosyphilis may cause no signs or symptoms, or it can cause:
    - Headache
    - Behavior changes
    - Movement problems

Clinical Prevention Guidance

- Prevention and control of STIs are based on the following five major strategies (*3*):
    1. Accurate risk assessment and education and counseling of persons at risk regarding ways to avoid STIs through changes in sexual behaviors and use of recommended prevention services
    2. Pre-exposure vaccination for vaccine-preventable STIs
    3. Identification of persons with an asymptomatic infection and persons with symptoms associated with an STI
    4. Effective diagnosis, treatment, counseling, and follow-up of persons who are infected with an STI
    5. Evaluation, treatment, and counseling of sex partners of persons who are infected with an STI

STI and HIV Infection Risk Assessment

- Primary prevention of STIs includes assessment of behavioral risk (i.e., assessing the sexual behaviors that can place persons at risk for infection) and biologic risk (i.e., testing for risk markers for STI and HIV acquisition or transmission).
- Primary prevention of STIs includes assessment of behavioral risk (i.e., assessing the sexual behaviors that can place persons at risk for infection) and biologic risk (i.e., testing for risk markers for STI and HIV acquisition or transmission
- **The Five P's approach for health care providers obtaining sexual histories: partners, practices, protection from sexually transmitted infections, past history of sexually transmitted infections, and pregnancy intention**
- **1. Partners**
    - "Are you currently having sex of any kind?"
    - "What is the gender(s) of your partner(s)?"
- 2. Practices
    - "To understand any risks for sexually transmitted infections (STIs), I need to ask more specific questions about the kind of sex you have had recently."
    - "What kind of sexual contact do you have or have you had?" "Do you have vaginal sex, meaning 'penis in vagina' sex?"
    - "Do you have anal sex, meaning 'penis in rectum/anus' sex?"
    - "Do you have oral sex, meaning 'mouth on penis/vagina'?"
- 3. Protection from STIs
    - "Do you and your partner(s) discuss prevention of STIs and human immunodeficiency virus (HIV)?"
    - "Do you and your partner(s) discuss getting tested?"
    - For condoms: "What protection methods do you use? In what situations do you use condoms?"
- 4. Past history of STIs
    - "Have you ever been tested for STIs and HIV?"
    - "Have you ever been diagnosed with an STI in the past?"
    - "Have any of your partners had an STI?"
    - Additional questions for identifying HIV and viral hepatitis risk:
    - "Have you or any of your partner(s) ever injected drugs?"
    - "Is there anything about your sexual health that you have questions about?"
- 5. Pregnancy intention
    - "Do you think you would like to have (more) children in the future?"

- "How important is it to you to prevent pregnancy (until then)?"
- "Are you or your partner using contraception or practicing any form of birth control?"
- "Would you like to talk about ways to prevent pregnancy?"

STI and HIV Infection Prevention Counseling

Primary Prevention Methods

Pre-Exposure Vaccination

- Pre-exposure vaccination is one of the most effective methods for preventing transmission of HPV, HAV, and HBV, all of which can be sexually transmitted Hepatitis B vaccination is recommended for all unvaccinated, uninfected persons who are sexually active with more than one partner or are being evaluated or treated for an STI (*12*). In addition, hepatitis A and B vaccines are recommended for MSM, persons who inject drugs, persons with chronic liver disease, and persons with HIV or hepatitis C infections who have not had hepatitis A or hepatitis B (*12*). HAV vaccine is also recommended for persons who are homeless

Condoms

- External Condoms
- When used consistently and correctly, external latex condoms, also known as male condoms, are effective in preventing the sexual transmission of HIV infection
- Internal Condoms
- Condoms for internal vaginal use, also known as female condoms, Use of internal condoms can provide protection from acquisition and transmission of STIs,

Cervical Diaphragms

- In observational studies, diaphragm use has been demonstrated to protect against cervical gonorrhea, chlamydia, and trichomoniasis

Emergency Contraception

- Unprotected intercourse exposes women to risks for STIs and unplanned pregnancy. Providers should offer counseling about the option of emergency contraception if pregnancy is not desired.

These guidelines are primarily limited to the identification

Urethral discharge

- Male patients complaining of urethral discharge and/or dysuria (pain during urination) should be examined for evidence of discharge. The major STIs causing urethral discharge are gonorrhea and chlamydia. In the syndromic management, treatment of a patient with urethral discharge should adequately cover these two STIs. Where reliable laboratory facilities are available, a distinction can be made between the two organisms and specific treatment instituted. Persistent or recurrent symptoms of urethritis (inflammation of the urethra) may result from drug resistance, poor compliance with the treatment or reinfection. Where symptoms persist or recur after adequate treatment for gonorrhea and chlamydia in the patient and his/her partner(s), the patient should be treated for trichomoniasis if cases of this STI is found in the geographical location of the patient.

Vaginal discharge

- A spontaneous complaint of abnormal vaginal discharge (in terms of quantity, color or odor) is most commonly a result of a vaginal infection but can also be caused by an STI such as chlamydia and gonorrhea. Detecting these STIs are difficult because a large proportion of women with gonorrhea or chlamydia are asymptomatic. Among women presenting with discharge, one can attempt to identify those with an increased likelihood of being infected with gonorrhea and/or chlamydia. To identify women at greater risk of having a STI, an assessment of a woman's risk

status may be useful, especially when risk factors are adapted to the local situation. Knowledge of the local prevalence of gonorrhea and/or chlamydia in women presenting with vaginal discharge is important when making the decision to treat for STI. The higher the prevalence, the stronger the justification for treatment. Women with a positive risk assessment have a higher likelihood of cervical infection than those who are risk negative. Women with vaginal discharge and a positive risk assessment should, therefore, be offered treatment for gonorrhea and chlamydia.

- In some countries, syndromic management flowcharts have been used as a screening tool to detect STIs among women not presenting with a genital complaint (e.g. in family planning settings). While this may assist in detecting some women with STIs, it is likely that there will be substantial overdiagnosis.

Genital Ulcer Disease (GUD)

- The relative prevalence of infections causing genital ulcers varies considerably in different parts of the world and may change dramatically over time. Distinguishing between diseases with similar symptoms of genital ulcers is often inaccurate. Symptoms and patterns of genital ulcers may be further changed in the presence of HIV infection.
- After examination to confirm the presence of genital ulcers, treatment appropriate to local settings and antimicrobial sensitivity patterns should be given. In areas where both syphilis and chancroid are prevalent, for example, patients with genital ulcers should be treated for both conditions at the time of their initial presentation, to ensure adequate therapy in case of loss to follow-up.
- Prompt and appropriate treatment with the following regimens is critical to avoid severe health complications:
    - Chlamydia:
        - Doxycycline is now the first-line recommended treatment; 100 mg orally twice a day for 7 days.
    - Trichomoniasis:
        - Metronidazole is recommended for treating all women; 500 mg orally twice a day for 7 days.
    - PID:
        - The recommended outpatient regimen is ceftriaxone 500 mg intramuscularly in a single dose + doxycycline 100 mg orally twice a day for 14 days + metronidazole 500 mg orally twice a day for 14 days.
- Providers should treat uncomplicated gonorrhea among adolescents and adults with a single 500 mg injection of ceftriaxone and, if chlamydia has not been ruled out, treat with 100 mg doxycycline orally twice a day for 7 days. A test of cure is recommended in people with pharyngeal gonorrhea. Either a culture or a nucleic acid amplification test (NAAT) is recommended, 7-14 days after the initial treatment, regardless of the regimen. Providers should retest patients 3 months after treatment to detect possible reinfection.
- Prompt testing and treatment are key to managing nongonococcal urethritis (NGU)

Specific infections and their treatments

Diseases Characterized by Genital, Anal, or Perianal Ulcers

- The majority of young, sexually active patients who have genital, anal, or perianal ulcers have either genital herpes or syphilis.
- More than one etiologic agent (e.g., herpes and syphilis) can be present in any genital, anal, or perianal ulcer. Less common infectious causes of genital, anal, or perianal ulcers include chancroid, LGV, and granuloma inguinale (donovanosis). GUDs (e.g., syphilis, herpes, and LGV) might also present as oral ulcers. Genital herpes, syphilis, chlamydia, gonorrhea, and chancroid have been associated with an increased risk for HIV acquisition and transmission. Genital, anal, or perianal lesions can also be

Chancroid

- The combination of one or more deep and painful genital ulcers and tender suppurative inguinal adenopathy indicates the chancroid diagnosis; inguinal lymphadenitis typically occurs in <50% of cases

Treatment

- Successful antimicrobial treatment for chancroid cures the infection, resolves the clinical symptoms, and prevents transmission to others. In advanced cases, genital scarring and rectal or urogenital fistulas from suppurative buboes can result despite successful therapy.
- Recommended Regimens for Chancroid
    - Azithromycin 1 g orally in a single dose
        - or
    - Ceftriaxone 250 mg IM in a single dose
        - or
    - Ciprofloxacin 500 mg orally 2 times/day for 3 days
        - or
    - Erythromycin base 500 mg orally 3 times/day for 7 days

Genital Herpes

- Genital herpes is a chronic, lifelong viral infection. Two types of HSV can cause genital herpes: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2, and 11.9% of persons aged 14–49 years are estimated to be infected in the United States (*436*). However, an increasing proportion of anogenital herpetic infections have been attributed to HSV-1, which is especially prominent among young women and MSM (*186*,*437*,*438*).
- The majority of persons infected with HSV-2 have not had the condition diagnosed, many of whom have mild or unrecognized infections but shed virus intermittently in the anogenital area. Consequently, most genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs. Management of genital HSV should address the chronic nature of the infection rather than focusing solely on treating acute episodes of genital lesions.
- Recommended Regimens for First Clinical Episode of Genital Herpes*
    - Acyclovir† 400 mg orally 3 times/day for 7–10 days
        - or
    - Famciclovir 250 mg orally 3 times/day for 7–10 days
        - or
    - Valacyclovir 1 g orally 2 times/day for 7–10 days
- * Treatment can be extended if healing is incomplete after 10 days of therapy.
- † Acyclovir 200 mg orally 5 times/day is also effective but is not recommended because of the frequency of dosing.

Recurrent HSV-2 Genital Herpes

- Almost all persons with symptomatic first-episode HSV-2 genital herpes subsequently experience recurrent episodes of genital lesions. Intermittent asymptomatic shedding occurs among persons with HSV-2 genital herpes infection, even those with longstanding clinically silent infection. Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions
- Recommended Regimens for **Suppression of Recurrent HSV-2 Genital Herpes**
    - Acyclovir 400 mg orally 2 times/day
        - or
    - Valacyclovir 500 mg orally once a day*
        - or
    - Valacyclovir 1 g orally once a day
        - or

    - Famciclovir 250 mg orally 2 times/day
- * Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year).
- Recommended Regimens for **Episodic Therapy for Recurrent HSV-2 Genital Herpes***
    - Acyclovir 800 mg orally 2 times/day for 5 days
        - or
    - Acyclovir 800 mg orally 3 times/day for 2 days
        - or
    - Famciclovir 1 g orally 2 times/day for 1 day
        - or
    - Famciclovir 500 mg orally once, followed by 250 mg 2 times/day for 2 days
        - or
    - Famciclovir 125 mg orally 2 times/day for 5 days
        - or
    - Valacyclovir 500 mg orally 2 times/day for 3 days
        - or
    - Valacyclovir 1 g orally once daily for 5 days
- Acyclovir 400 mg orally 3 times/day for 5 days is also effective but is not recommended because of frequency of dosing.
- Recommended Regimen for **Suppression of Recurrent Genital Herpes Among Pregnant Women***
    - Acyclovir 400 mg orally 3 times/day
        - or
    - Valacyclovir 500 mg orally 2 times/day
- * Treatment recommended starting at 36 weeks' gestation.

Granuloma Inguinale (Donovanosis)

- Granuloma inguinale (donovanosis) is a genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*Granuloma Inguinale (Donovanosis)
- Granuloma inguinale (donovanosis) is a genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*).
- Recommended Regimen for Granuloma Inguinale (Donovanosis)
    - Azithromycin 1 g orally once/week or 500 mg daily for >3 weeks and until all lesions have completely healed
- Alternative Regimens
    - Doxycycline 100 mg orally 2 times/day for at least 3 weeks and until all lesions have completely healed
        - or
    - Erythromycin base 500 mg orally 4 times/day for >3 weeks and until all lesions have completely healed
        - or
    - Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally 2 time/day for >3 weeks and until all lesions have completely healed

Lymphogranuloma Venereum

- LGV is caused by *C. trachomatis* serovars L1, L2, or L3 (*539*,*540*). LGV can cause severe inflammation and invasive infection, in contrast with *C. trachomatis* serovars A–K that cause mild or asymptomatic infection. Clinical manifestations of LGV can include GUD, lymphadenopathy, or proctocolitis. Rectal exposure among MSM or women can result in proctocolitis, which is the most common presentation of LGV infection (*541*), and can mimic inflammatory bowel disease

with clinical findings of mucoid or hemorrhagic rectal discharge, anal pain, constipation, fever, or tenesmus

- Recommended Regimen for Lymphogranuloma Venereum
    - Doxycycline 100 mg orally 2 times/day for 21 days
- Alternative Regimens
    - Azithromycin 1 g orally once weekly for 3 weeks*
        - or
    - Erythromycin base 500 mg orally 4 times/day for 21 days
- Because this regimen has not been validated, a test of cure with *C. trachomatis* NAAT 4 weeks after completion of treatment can be considered

Syphilis

- Syphilis is a systemic disease caused by *T. pallidum*
- Primary syphilis classically presents as a single painless ulcer or chancre at the site of infection but can also present with multiple, atypical, or painful lesions (*564*). Secondary syphilis manifestations can include skin rash, mucocutaneous lesions, and lymphadenopathy. Tertiary syphilis can present with cardiac involvement, gummatous lesions, tabes dorsalis, and general paresis
- Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are classified as late latent syphilis or latent syphilis of unknown duration.
- *T. pallidum* can infect the CNS, which can occur at any stage of syphilis and result in neurosyphilis. Early neurologic clinical manifestations or syphilitic meningitis (e.g., cranial nerve dysfunction, meningitis, meningovascular syphilis, stroke, and acute altered mental status) are usually present within the first few months or years of infection. Late neurologic manifestations (e.g., tabes dorsalis and general paresis) occur 10 to >30 years after infection.
- Infection of the visual system (ocular syphilis) or auditory system (otosyphilis) can occur at any stage of syphilis but is commonly identified during the early stages and can present with or without additional CNS involvement. Ocular syphilis often presents as panuveitis but can involve structures in both the anterior and posterior segment of the eye, including conjunctivitis, anterior uveitis, posterior interstitial keratitis, optic neuropathy, and retinal vasculitis. Ocular syphilis can result in permanent vision loss. Otosyphilis typically presents with cochleo-vestibular symptoms, including tinnitus, vertigo, and sensorineural hearing loss. Hearing loss can be unilateral or bilateral, have a sudden onset, and progress rapidly. Otosyphilis can result in permanent hearing loss.
- Recommended Regimen for **Primary and Secondary Syphilis* Among Adults**
    - Benzathine penicillin G 2.4 million units IM in a single dose
- * Recommendations for treating syphilis among persons with HIV infection and pregnant women are discussed elsewhere in this report (see Syphilis Among Persons with HIV Infection; Syphilis During Pregnancy).
- Recommended Regimen for **Syphilis Among Infants and Children**
    - Benzathine penicillin G 50,000 units/kg body weight IM, up to the adult dose of 2.4 million units in a single dose
- Recommended Regimens for **Latent Syphilis* Among Adults**
- Early latent syphilis:
    - Benzathine penicillin G 2.4 million units IM in a single dose
- Late latent syphilis:
    - Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
- Recommendations for treating syphilis in persons with HIV and pregnant women are discussed elsewhere in this report (see Syphilis Among Persons with HIV Infection; Syphilis During Pregnancy
- Recommended Regimen for **Tertiary Syphilis Among Adults**

- Tertiary syphilis with *normal CSF examination*:
    - Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
- Recommended Regimen for **Neurosyphilis, Ocular Syphilis, or Otosyphilis Among Adults**
    - Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion for 10–14 days
- Alternative Regimen
    - Procaine penicillin G 2.4 million units IM once daily
    - plus
    - Probenecid 500 mg orally 4 times/day, both for 10–14 days
- Recommended Regimen for ***Syphilis During Pregnancy***
    - Pregnant women should be treated with the recommended penicillin regimen for their stage of infection
    - Recommended Regimens, Confirmed or Highly Probable Congenital Syphilis
    - Aqueous crystalline penicillin G 100,000–150,000 units/kg/body weight/day, administered as 50,000 units/kg body weight/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
        - or
    - Procaine penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days

Diseases Characterized by Urethritis and Cervicitis

Urethritis

- Urethritis, as characterized by urethral inflammation, can result from either infectious or noninfectious conditions. Symptoms, if present, include dysuria, urethral pruritis, and mucoid, mucopurulent, or purulent discharge. Signs of urethral discharge on examination can also be present among persons without symptoms. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *M. genitalium* has been strongly associated with urethritis and, less commonly, prostatitis
- Adenovirus can present with dysuria, meatal inflammation, and conjunctivitis. Other bacterial pathogens have been implicated as potential causes of clinical urethritis, either in clustered case series or as sporadic cases such as *Haemophilus influenzae* and *Haemophilus parainfluenzae*

Nongonococcal Urethritis

- NGU is a nonspecific diagnosis that can have various infectious etiologies
- C. trachomatis
- Recommended Regimen for Nongonococcal Urethritis
    - Doxycycline 100 mg orally 2 times/day for 7 days
- Alternative Regimens
    - Azithromycin 1 g orally in a single dose
        - or
    - Azithromycin 500 mg orally in a single dose; then 250 mg orally daily for 4 days

Cervicitis

- Two major diagnostic signs characterize cervicitis:
    - 1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as mucopurulent cervicitis), and
    - 2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os
- Recommended Regimen for Cervicitis*

    - Doxycycline 100 mg orally 2 times/day for 7 days
- Consider concurrent treatment for gonococcal infection if the patient is at risk for gonorrhea or lives in a community where the prevalence of gonorrhea is high (see Gonococcal Infections).
- Alternative Regimen
    - Azithromycin 1 g orally in a single dose

Chlamydial Infections

- Chlamydial Infection Among Adolescents and Adults
- Multiple sequelae can result from *C. trachomatis* infection among women, the most serious of which include PID, ectopic pregnancy, and infertility. Certain women who receive a diagnosis of uncomplicated
- Recommended Regimen for **Chlamydial Infection Among Adolescents and Adults**
    - Doxycycline 100 mg orally 2 times/day for 7 days
- Alternative Regimens
    - Azithromycin 1 g orally in a single dose
        - or
    - Levofloxacin 500 mg orally once daily for 7 days
- Recommended Regimen for **Chlamydial Infection During Pregnancy**
    - Azithromycin 1 g orally in a single dose
- Alternative Regimen
    - Amoxicillin 500 mg orally 3 times/day for 7 days
- Recommended Regimens for **Chlamydial Infection Among Infants and Children**
- For infants and children weighing <45 kg:
    - Erythromycin base or ethyl succinate 50 mg/kg body weight/day orally divided into 4 doses daily for 14 days
- Data are limited regarding the effectiveness and optimal dose of azithromycin for treating chlamydial infection among infants and children weighing <45 kg.
- For children weighing ≥45 kg but aged <8 years:
    - Azithromycin 1 g orally in a single dose
- For children aged ≥8 years:
    - Azithromycin 1 g orally in a single dose
        - or
    - Doxycycline 100 mg orally 2 times/day for 7 days

Gonococcal Infections

- Gonococcal Infection Among Adolescents and Adults
- Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum
- Recommended Regimen for Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum **Among Adults and Adolescents**
    - Ceftriaxone 500 mg* IM in a single dose for persons weighing <150 kg
- If chlamydial infection has not been excluded, treat for chlamydia with
    - doxycycline 100 mg orally 2 times/day for 7 days.
- For persons weighing ≥150 kg,
    - 1 g ceftriaxone should be administered.
- Recommended Regimen for Gonococcal Conjunctivitis Among Adolescents and Adults
    - Ceftriaxone 1 g IM in a single dose
- Providers should consider one-time lavage of the infected eye with saline solution

Treatment of Gonococcal Meningitis and Endocarditis

- Recommended Regimen for Gonococcal Meningitis and Endocarditis
    - Ceftriaxone 1–2 g IV every 24 hours

- If chlamydial infection has not been excluded, providers should treat for chlamydia with
    - doxycycline 100 mg orally 2 times/day for 7 days.
- Recommended Regimen to Prevent Ophthalmia Neonatorum Caused by *N. gonorrhoeae*
    - Erythromycin 0.5% ophthalmic ointment in each eye in a single application at birth

Mycoplasma genitalium

- *M. genitalium* causes symptomatic and asymptomatic urethritis among men
- Diseases Characterized by Vulvovaginal Itching, Burning, Irritation, Odor, or Discharge
- The majority of women will have a vaginal infection, characterized by discharge, itching, burning, or odor, during their lifetime

Bacterial Vaginosis

- BV is a vaginal dysbiosis resulting from replacement of normal hydrogen peroxide and lactic-acid–producing *Lactobacillus* species in the vagina with high concentrations of anaerobic bacteria, including *G. vaginalis*, *Prevotella* species, *Mobiluncus* species, *A. vaginae*, and other BV-associated bacteria
- Recommended Regimens for Bacterial Vaginosis
    - Metronidazole 500 mg orally 2 times/day for 7 days
        - or
    - Metronidazole gel 0.75% one full applicator (5 g) intravaginally, once daily for 5 days
        - or
    - Clindamycin cream 2% one full applicator (5 g) intravaginally at bedtime for 7 days
- Alternative Regimens
    - Clindamycin 300 mg orally 2 times/day for 7 days
        - or
    - Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days*
        - or
    - Secnidazole 2 g oral granules in a single dose†
        - or
    - Tinidazole 2 g orally once daily for 2 days
        - or
    - Tinidazole 1 g orally once daily for 5 days
- * Clindamycin ovules use an oleaginous base

Vulvovaginal Candidiasis

- VVC usually is caused by *Candida albicans* but can occasionally be caused by other *Candida* species or yeasts. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge.
- Recommended Regimens for Vulvovaginal Candidiasis
    - Over-the-Counter Intravaginal Agents
        - Clotrimazole 1% cream 5 g intravaginally daily for 7–14 days
            - or
        - Clotrimazole 2% cream 5 g intravaginally daily for 3 days
            - or
        - Miconazole 2% cream 5 g intravaginally daily for 7 days
            - or
        - Miconazole 4% cream 5 g intravaginally daily for 3 days
            - or
        - Miconazole 100 mg vaginal suppository one suppository daily for 7 days
            - or
        - Miconazole 200 mg vaginal suppository one suppository for 3 days

        - or
      - Miconazole 1,200 mg vaginal suppository one suppository for 1 day
        - or
      - Tioconazole 6.5% ointment 5 g intravaginally in a single application
    - Prescription Intravaginal Agents
      - Butoconazole 2% cream (single-dose bioadhesive product) 5 g intravaginally in a single application
        - or
      - Terconazole 0.4% cream 5 g intravaginally daily for 7 days
        - or
      - Terconazole 0.8% cream 5 g intravaginally daily for 3 days
        - or
      - Terconazole 80 mg vaginal suppository one suppository daily for 3 days
    - Oral Agent
      - Fluconazole 150 mg orally in a single dose

Pelvic Inflammatory Disease

- Pelvic inflammatory disease (PID) is an infectious and inflammatory disorder of the upper female genital tract, including the uterus, fallopian tubes, and adjacent pelvic structures. Infection and inflammation may spread to the abdomen, including perihepatic structures (Fitz-Hugh−Curtis syndrome). The classic high-risk patient is a menstruating woman younger than 25 years who has multiple sex partners, does not use contraception, and lives in an area with a high prevalence of sexually transmitted disease (STD).
- Signs and symptoms of pelvic inflammatory disease
- The diagnosis of acute PID is primarily based on historical and clinical findings. Clinical manifestations of PID vary widely. Many patients exhibit few or no symptoms, whereas others have acute, serious illness. The most common presenting complaint is lower abdominal pain. Many women report an abnormal vaginal discharge.
- Diagnosis of pelvic inflammatory disease

Differential diagnosis

- includes appendicitis, cervicitis, urinary tract infection, endometriosis, ovarian torsion, and adnexal tumors. Ectopic pregnancy can be mistaken for PID; indeed, PID is the most common incorrect diagnosis in cases of ectopic pregnancy. Consequently, a pregnancy test is mandatory in the workup of women of childbearing age who have lower abdominal pain.
- PID may produce tubo-ovarian abscess (TOA) and may progress to peritonitis and Fitz-Hugh−Curtis syndrome (perihepatitis;). [1] Note that a rare but life-threatening complication of acute rupture of a TOA may result in diffuse peritonitis and necessitate urgent abdominal surgery.

Treatment

- PID treatment regimens should provide empiric, broad-spectrum coverage of likely pathogens. Multiple parenteral and oral antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short-term follow-up
- Recommended Parenteral Regimens for Pelvic Inflammatory Disease
  - Ceftriaxone 1 g by every 24 hours
  - plus
  - Doxycycline 100 mg orally or IV every 12 hours
  - plus
  - Metronidazole 500 mg orally or IV every 12 hours
    - or
  - Cefotetan 2 g IV every 12 hours
  - plus

    - Doxycycline 100 mg orally or IV every 12 hours
        - or
    - Cefoxitin 2 g IV every 6 hours
    - plus
    - Doxycycline 100 mg orally or IV every 12 hours
- Alternative Parenteral Regimens
    - Ampicillin-sulbactam 3 g IV every 6 hours
    - plus
    - Doxycycline 100 mg orally or IV every 12 hours
        - or
    - Clindamycin 900 mg IV every 8 hours
    - plus
    - Gentamicin loading dose IV or IM (2 mg/kg body weight), followed by a maintenance dose (1.5 mg/kg body weight) every 8 hours; single daily dosing (3–5 mg/kg body weight) can be substituted
- Recommended Intramuscular or Oral Regimens for Pelvic Inflammatory Disease
    - Ceftriaxone 500 mg* IM in a single dose
    - plus
    - Doxycycline 100 mg orally 2 times/day for 14 days with metronidazole 500 mg orally 2 times/day for 14 days
        - or
    - Cefoxitin 2 g IM in a single dose and probenecid 1 g orally administered concurrently in a single dose
    - plus
    - Doxycycline 100 mg orally 2 times/day for 14 days with metronidazole 500 mg orally 2 times/day for 14 days
        - or
    - Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
    - plus
    - Doxycycline 100 mg orally 2 times/day for 14 days with metronidazole 500 mg orally 2 times/day for 14 days
- * For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered

Epididymitis

- Acute epididymitis is a clinical syndrome causing pain, swelling, and inflammation of the epididymis and lasting <6 weeks (*1191*). Sometimes a testicle is also involved, a condition referred to as epididymo-orchitis
- Acute epididymitis can be caused by STIs (e.g., *C. trachomatis, N. gonorrhoeae*, or *M. genitalium*) or enteric organisms (i.e., *Escherichia coli*) (*1192*). Acute epididymitis caused by an STI is usually accompanied by urethritis, which is frequently asymptomatic. Acute epididymitis caused by sexually transmitted enteric organisms might also occur among men who are the insertive partner during anal sex.
- Nonsexually transmitted acute epididymitis caused by genitourinary pathogens typically occurs with bacteriuria secondary to bladder outlet obstruction (e.g., benign prostatic hyperplasia
- Recommended Regimens for Epididymitis
- For acute epididymitis most likely caused by chlamydia or gonorrhea:
    - Ceftriaxone 500 mg* IM in a single dose
    - plus
    - Doxycycline 100 mg orally 2 times/day for 10 days
- For acute epididymitis **most likely caused by chlamydia, gonorrhea, or enteric organisms (men who practice insertive anal sex):**
    - Ceftriaxone 500 mg* IM in a single dose

    - plus
    - Levofloxacin 500 mg orally once daily for 10 days
- For acute epididymitis most likely caused by enteric organisms only:
    - Levofloxacin 500 mg orally once daily for 10 days
- * For persons weighing ≥150 kg,
    - 1 g of ceftriaxone should be
- Levofloxacin monotherapy should be considered if the infection is most likely caused by enteric organisms only, and gonorrhea has been ruled out by Gram, MB, or GV stain

Human Papillomavirus Infections

- Approximately 150 types of HPV have been identified, at least 40 of which infect the genital area (*1194*). The majority of HPV infections are self-limited and are asymptomatic or unrecognized. Sexually active persons are usually exposed to HPV during their lifetime

Treatment

- Treatment is directed to the macroscopic (e.g., genital warts) or pathologic precancerous lesions caused by HPV. Subclinical genital HPV infection typically clears spontaneously; therefore, specific antiviral therapy is not recommended to eradicate HPV infection.
- Precancerous lesions are detected through cervical cancer screening; HPV-related precancer should be managed on the basis of existing guidance (see Cervical Cancer).

Anogenital Warts

- Anogenital warts are a common disease, and 90% are caused by nononcogenic HPV types 6 or 11. These types can be commonly identified before or at the same time anogenital warts are detected

Treatment

- The aim of treatment is removal of the warts and amelioration of symptoms, if present
    - Surgical removal by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery
        - or
    - Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution
- Persons with external anal or perianal warts might also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy.
- Might weaken condoms and vaginal diaphragms.
- Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus)*
- Patient-applied:
    - Imiquimod 3.75% or 5% cream†
        - or
    - Podofilox 0.5% solution or gel
        - or
    - Sinecatechins 15% ointment†
- Provider-administered:
    - Cryotherapy with liquid nitrogen or cryoprobe
- Recommended Regimens for Urethral Meatus Warts
    - Cryotherapy with liquid nitrogen
        - or
    - Surgical removal

Cancers and Precancers Associated with Human Papillomavirus

- Persistent infection with high-risk (oncogenic) types of HPV has a causal role in approximately all cervical cancers and in certain vulvar, vaginal, penile, anal, and oropharyngeal cancers (*1238*). However, cervical cancer is the only HPV-associated cancer for which routine screening is recommended

Prevention

- Three HPV vaccines can prevent diseases and cancers caused by HPV

Treatment

- Treatment is directed to the macroscopic (e.g., genital warts) or pathologic precancerous lesions caused by HPV. Subclinical genital HPV infection typically clears spontaneously; therefore, specific antiviral therapy is not recommended to eradicate HPV infection. Precancerous lesions are detected through cervical cancer screening; HPV-related precancer should be managed on the basis of existing guidance

Cervical Cancer

- Recommendations for cervical cancer screening. Clinics should weigh the benefits of each screening strategy as well as their resources, such as time and cost.
- The following additional management considerations are associated with performing Pap tests and HPV tests:
    - Cytology (Pap tests) and HPV tests should not be considered screening tests for STIs.
- All persons with a cervix should receive cervical cancer screening, regardless of sexual orientation or gender identity (i.e., those who identify as lesbian, bisexual, heterosexual, or transgender).
- A conventional cytology test (in which the sample is smeared onto a dry slide) should ideally be scheduled for 10–20 days after the first day of menses. Liquid-based cytology can be performed at any time during the menstrual cycle.
- If specific infections other than HPV (e.g., chlamydia or gonorrhea) are identified at the visit, a repeat cytology test after appropriate treatment for those infections might be indicated. However, in most instances (even in the presence of certain severe cervical infections), cytology tests will be reported as satisfactory for evaluation, and reliable final reports can be produced without the need to repeat the cytology test after treatment.

Proctitis, Proctocolitis, and Enteritis

- Sexually transmitted gastrointestinal syndromes include proctitis, proctocolitis, and enteritis. Evaluation for these syndromes should include recommended diagnostic procedures, including anoscopy or sigmoidoscopy, stool examination for WBCs, and microbiologic workup (e.g., gonorrhea, chlamydia [LGV PCR if available], herpes simplex NAAT, and syphilis serology). For those with enteritis, stool culture or LGV PCR also is recommended.
- Proctitis is inflammation of the rectum (i.e., the distal 10–12 cm) that can be associated with anorectal pain, tenesmus, or rectal discharge. Fecal leukocytes are common. Proctitis occurs predominantly among persons who have receptive anal exposures (oral-anal, digital-anal, or genital-anal). *N. gonorrhoeae, C. trachomatis* (including LGV serovars), HSV, and *T. pallidum* are the most common STI pathogens. Genital HSV and LGV proctitis are more prevalent among persons with HIV infection (*545,556,1382*). *M. genitalium* has been detected in certain cases of proctitis and might be

Diagnostic and Treatment Considerations for Acute Proctitis

- Persons with symptoms of acute proctitis should be examined by anoscopy. A Gram-stained smear of any anorectal exudate from anoscopic or anal examination should be examined for polymorphonuclear leukocytes

- Recommended Regimen for Acute Proctitis
    - Ceftriaxone 500 mg* IM in a single dose
    - plus
    - Doxycycline 100 mg orally 2 times/day for 7 days†
- * For persons weighing ≥150 kg,
    - 1 g of ceftriaxone should be administered.
    - † Doxycycline course should be extended to 100 mg orally 2 times/day for 21 days in the presence of bloody discharge, perianal or mucosal ulcers, or tenesmus and a positive rectal chlamydia test.

Diagnostic and Treatment Considerations for Proctocolitis or Enteritis

- Treatment for proctocolitis or enteritis should be directed to the specific enteric pathogen identified. Multiple stool examinations might be necessary for detecting *Giardia*, and special stool preparations are required for diagnosing cryptosporidiosis and microsporidiosis.

Ectoparasitic Infections

Pediculosis Pubis

- Persons who have pediculosis pubis (i.e., pubic lice) usually seek medical attention because of pruritus or because they notice lice or nits on their pubic hair. Pediculosis pubis is caused by the parasite *Phthirus pubis* and is usually transmitted by sexual contact (*1393*).

Diagnosis

- The clinical diagnosis is based on typical symptoms of itching in the pubic region. Lice and nits can be observed on pubic hair

Treatment

- Recommended Regimens for Pediculosis Pubis
    - Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes
        - or
    - Pyrethrin with piperonyl butoxide applied to the affected area and washed off after 10 minutes
- Alternative Regimens
    - Malathion 0.5% lotion applied to affected areas and washed off after 8–12 hours
        - or
    - Ivermectin 250 μg/kg body weight orally, repeated in 7–14 days

Scabies

- Scabies is a skin infestation caused by the mite *Sarcoptes scabiei*, which causes pruritus. Sensitization to *S. scabiei* occurs before pruritus begins. The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop
- The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. Scabies amo
- Recommended Regimens for Scabies
    - Permethrin 5% cream applied to all areas of the body from the neck down and washed off after 8–14 hours
        - or
    - Ivermectin 200 ug/kg body weight orally, repeated in 14 days*
        - or
    - Ivermectin 1% lotion applied to all areas of the body from the neck down and washed off after 8–14 hours; repeat treatment in 1 week if symptoms persist
- * Oral ivermectin has limited ovicidal activity; a second dose is required for eradication.

Sexual Assault and Abuse and STIs

Adolescents and Adults

- These guidelines are primarily limited to the identification, prophylaxis, and treatment of STIs and conditions among adolescent and adult female sexual assault survivors Documentation of findings, collection of non microbiologic specimens for forensic purposes, and management of potential pregnancy or physical and psychological trauma are beyond the scope of these guidelines. Examinations of survivors of sexual assault should be conducted by an experienced clinician in a way that minimizes further trauma to the person. The decision to obtain genital or other specimens for STI diagnosis should be made on an individual basis.
- **Trichomoniasis, BV, gonorrhea, and chlamydia** are the most frequently diagnosed infections among women who have been sexually assaulted
- Recommended Regimen for Adolescent and Adult Female Sexual Assault Survivors
    - Ceftriaxone 500 mg* IM in a single dose
    - plus
    - Doxycycline 100 mg 2 times/day orally for 7 days
    - plus
    - Metronidazole 500 mg 2 times/day orally for 7 days
- For persons weighing ≥150 kg,
    - 1 g of ceftriaxone should be
- Recommended Regimen for Adolescent and Adult Male Sexual Assault Survivors
    - Ceftriaxone 500 mg* IM in a single dose
    - plus
    - Doxycycline 100 mg 2 times/day orally for 7 days
- For persons weighing ≥150 kg,
    - 1 g of ceftriaxone should be administered.

Reference:

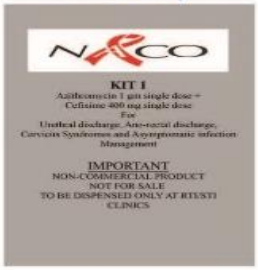
1. STI Guideline 2021
2. WHO Guideline
3. https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcQpBJilC9Ep9rDnnQ08UuA_UA_chj8rEOe67g&usqp=CAU
4. https://data.unhcr.org/images/documents/big_3557cf4ee194e26dc3a500b6db4c154a4b32bb5e.jpg

Urethral Discharge

- Urethral Discharge (Pus or muco-purulent)
- Pain or burning while passing urine
- Increased frequency of urination
- Systemic symptoms like malaise, fever

Tab. Azithromycin 1 gm
OD Stat +
Tab. Cefixime 400 mg
OD Stat

KIT 1/Grey



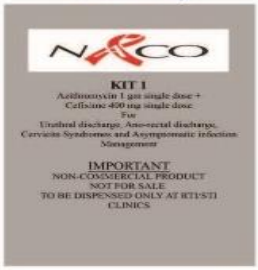
Treat all recent partners

Cervical Discharge

- Nature and type of discharge (quantity, color and odor)
- Burning while passing urine, increased frequency
- Genital complaints by sexual partners
- Low backache
  (Take menstrual history to rule out pregnancy)

Tab. Azithromycin 1 gm
OD Stat +
Tab. Cefixime 400 mg
OD Stat

KIT 1/Grey



Treat partners when symptomatic

Painful Scrotal Swelling

- Swelling and pain in the scrotal region
- Pain or burning while passing urine
- Systemic symptoms like malaise, fever
- History of urethral discharge

Tab. Azithromycin 1 gm
OD Stat +
Tab. Cefixime 400 mg
OD Stat

KIT 1/Grey

Treat all recent partners

Vaginal Discharge

- Nature and type of discharge (quantity, color and odor)
- Burning while passing urine, increased frequency
- Genital complaints by sexual partners
- Low backache
  (Take menstrual history to rule out pregnancy)

Tab. Secnidazole 2 g
OD Stat +
Cap. Fluconazole 150 mg
OD Stat

KIT 2/Green

Treat partners when symptomatic

Genital Ulcer-Non Herpetic

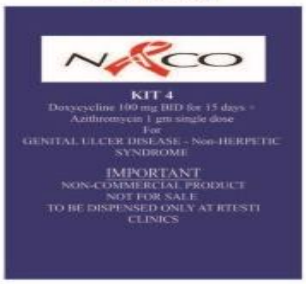
- Genital ulcer, single or multiple, painful or painless
- Burning sensation in the genital area
- Enlarged lymph nodes

Inj. Benzathine penicillin
(2.4 MU) - 1 vial
Tab. Azithromycin (1 gm) -
Single dose

KIT 3/White

If allergic to Inj. Penicillin:
Doxycycline 100 MG
(Bid for 15 days)
Azithromycin 1GM (Single dose)

KIT 4/Blue



Treat all sexual partners for past 3 months

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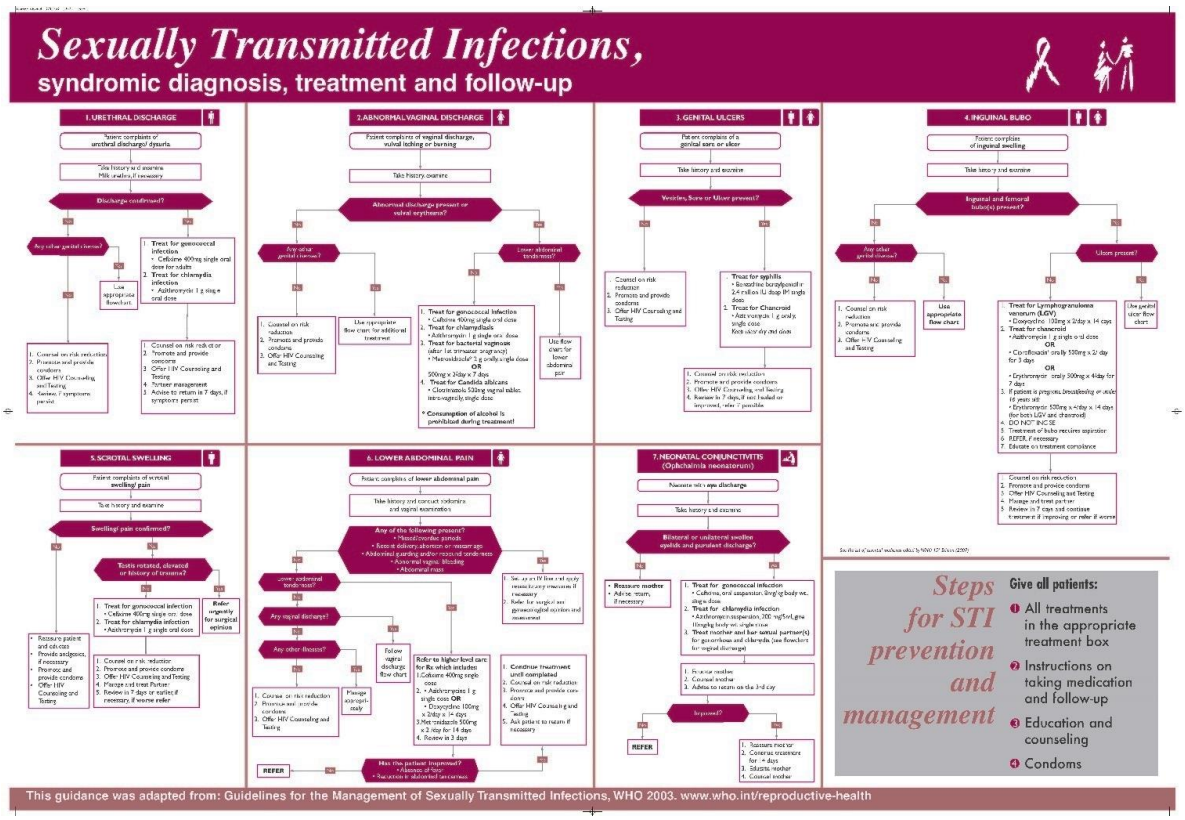

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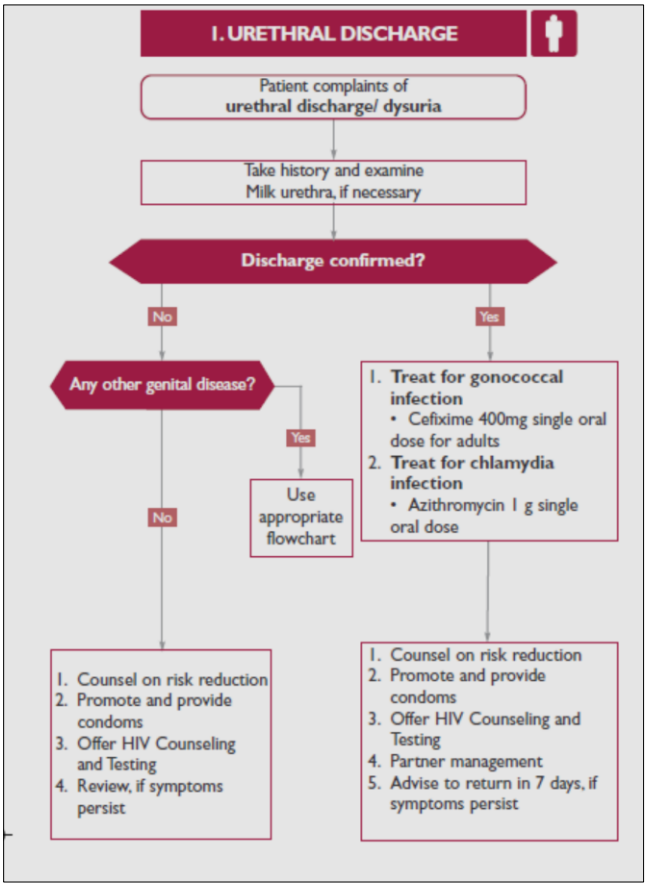
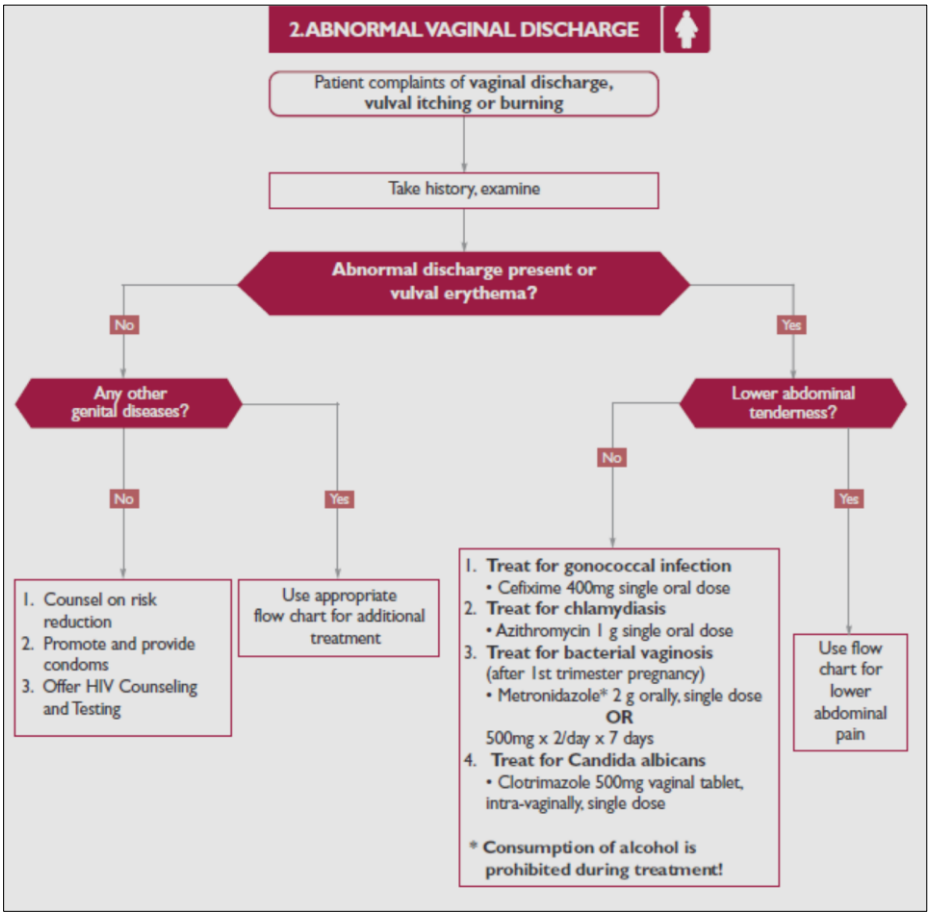
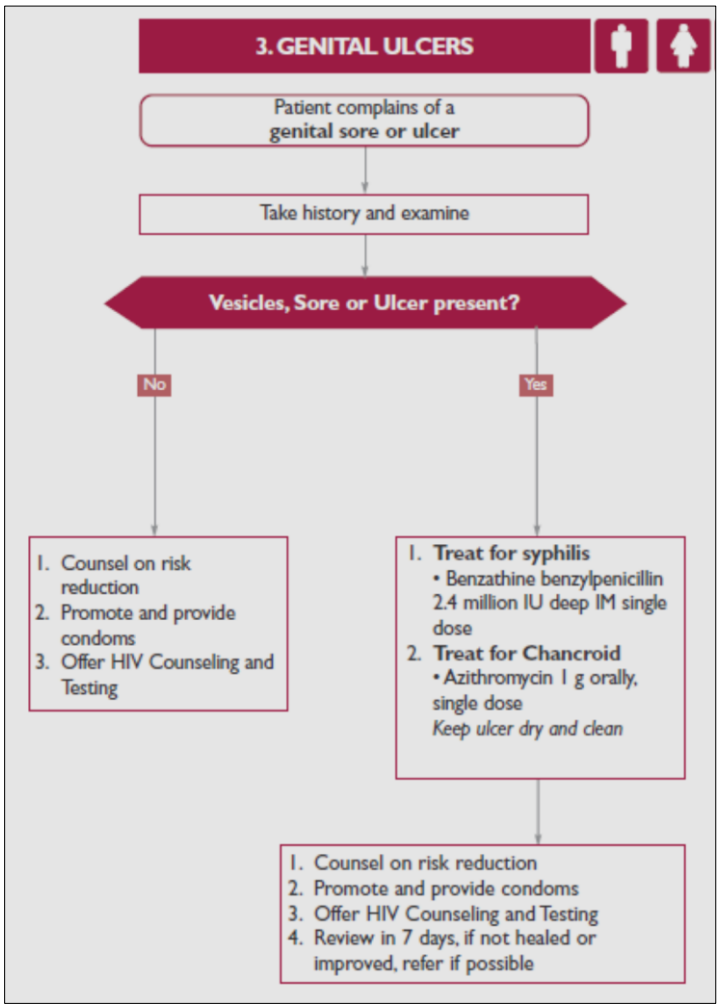
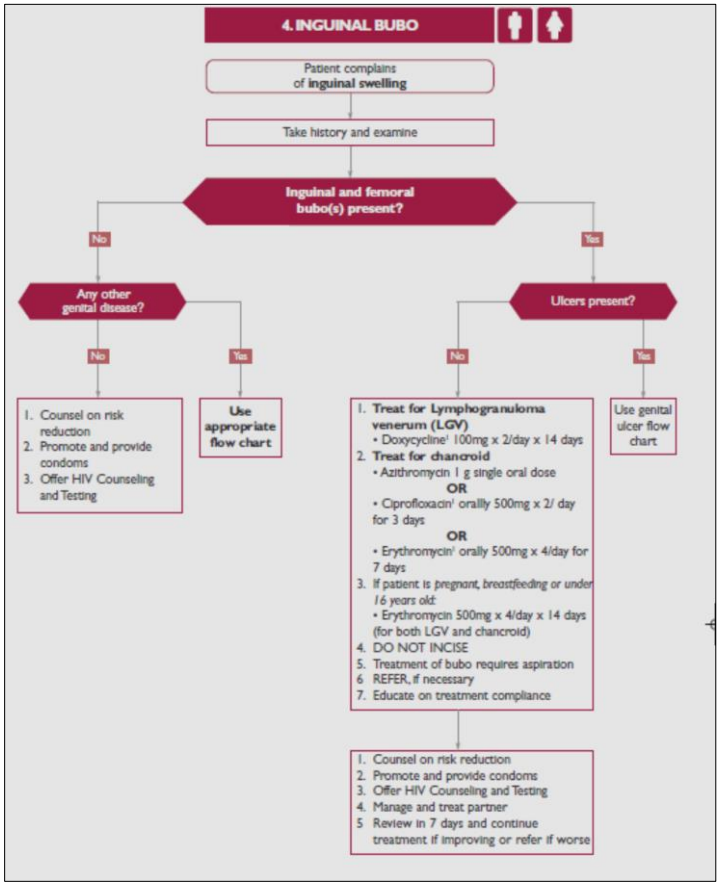
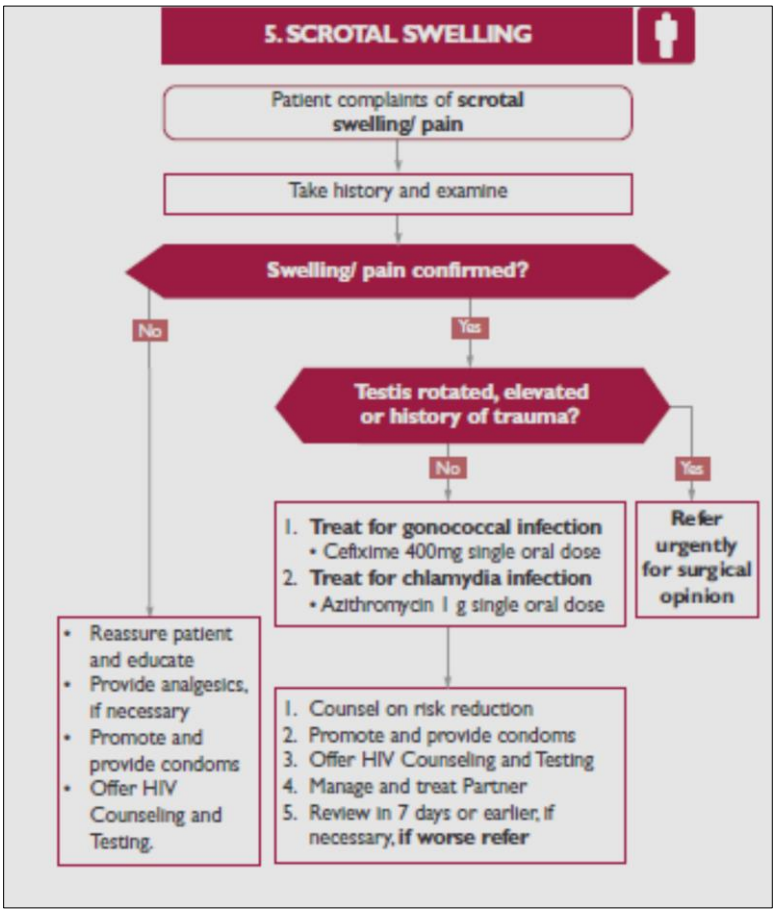
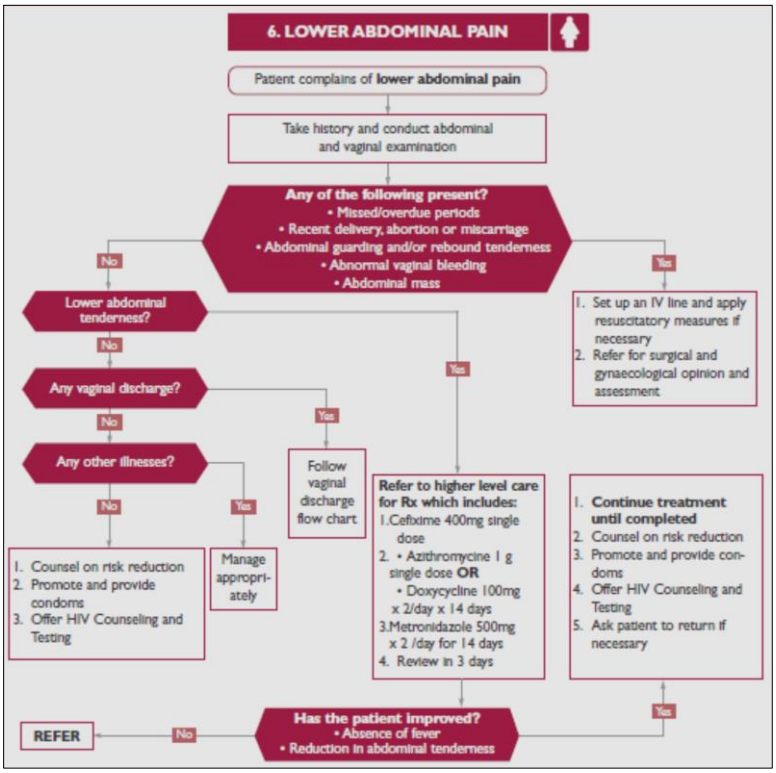


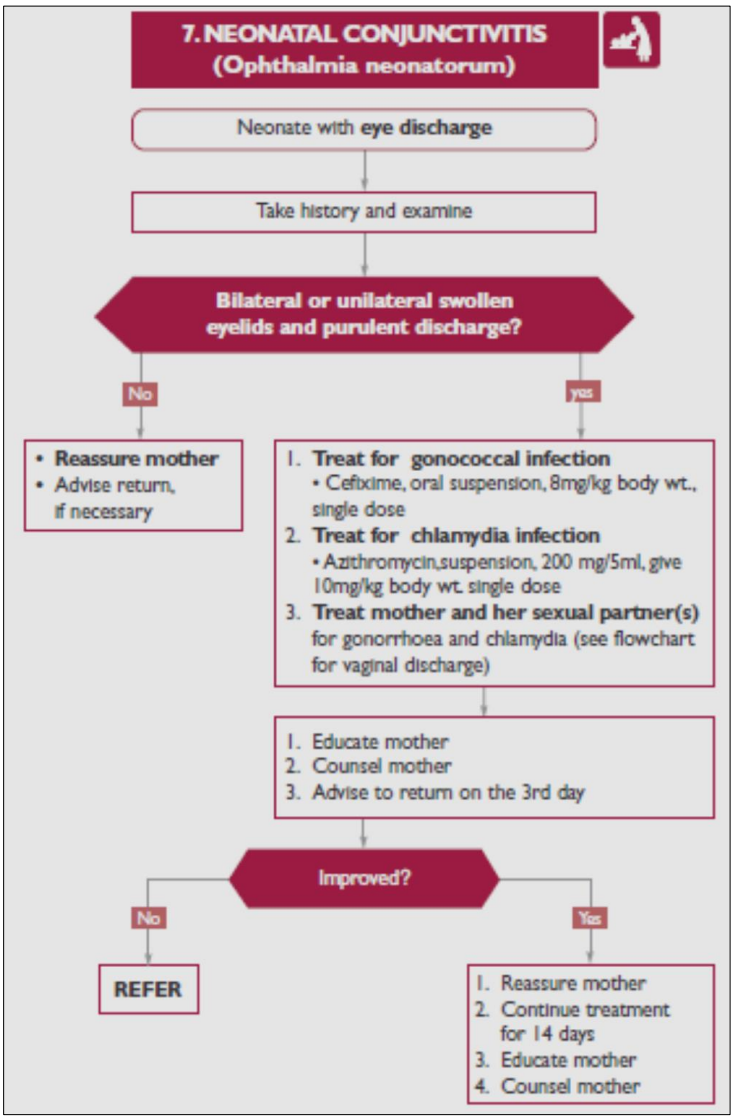



3. GENITAL ULCERS
Patient complains of a genital sore or ulcer
Take history and examine
Vesicles, Sore or Ulcer present?
No
Yes
1. Counsel on risk reduction
2. Promote and provide condoms
3. Offer HIV Counseling and Testing
1. Treat for syphilis
• Benzathine benzylpenicillin 2.4 million IU deep IM single dose
2. Treat for Chancroid
• Azithromycin 1 g orally, single dose
Keep ulcer dry and clean
1. Counsel on risk reduction
2. Promote and provide condoms
3. Offer HIV Counseling and Testing
4. Review in 7 days, if not healed or improved, refer if possible


4. INGUINAL BUBO
Patient complains of inguinal swelling
Take history and examine
Inguinal and femoral bubo(s) present?
No
Yes
Any other genital disease?
Ulcers present?
No
Yes
No
Yes
1. Counsel on risk reduction
2. Promote and provide condoms
3. Offer HIV Counseling and Testing
Use appropriate flow chart
1. Treat for Lymphogranuloma venerum (LGV)
• Doxycycline¹ 100mg x 2/day x 14 days
2. Treat for chancroid
• Azithromycin 1 g single oral dose
OR
• Ciprofloxacin¹ orallly 500mg x 2/ day for 3 days
OR
• Erythromycin¹ orally 500mg x 4/day for 7 days
3. If patient is pregnant, breastfeeding or under 16 years old:
• Erythromycin 500mg x 4/day x 14 days (for both LGV and chancroid)
4. DO NOT INCISE
5. Treatment of bubo requires aspiration
6 REFER, if necessary
7. Educate on treatment compliance
Use genital ulcer flow chart
1. Counsel on risk reduction
2. Promote and provide condoms
3. Offer HIV Counseling and Testing
4. Manage and treat partner
5 Review in 7 days and continue treatment if improving or refer if worse

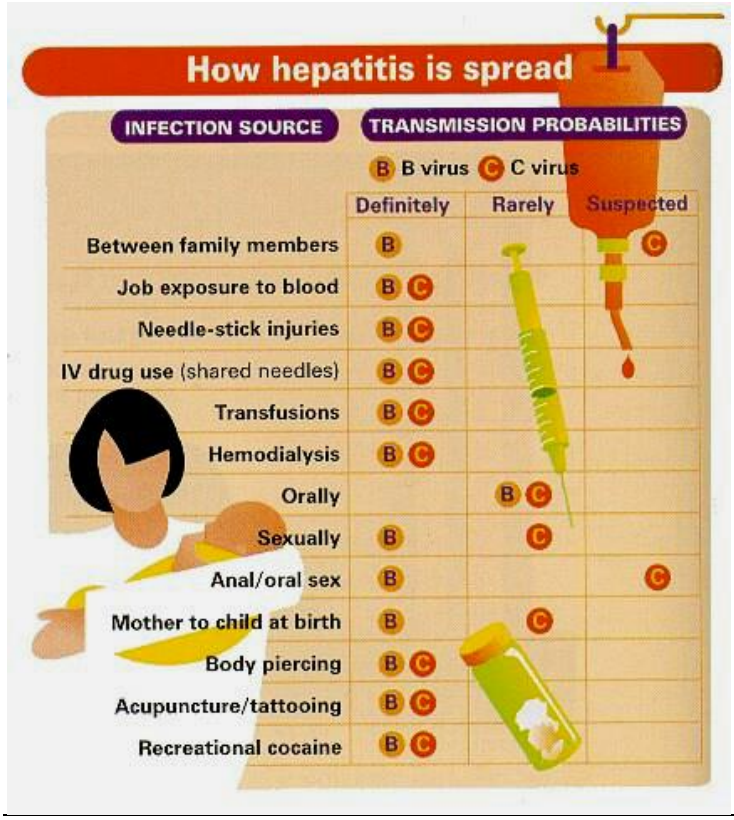

5. SCROTAL SWELLING
Patient complaints of scrotal swelling/ pain
Take history and examine
Swelling/ pain confirmed?
No
Yes
Testis rotated, elevated or history of trauma?
No
Yes
1. Treat for gonococcal infection
• Cefixime 400mg single oral dose
2. Treat for chlamydia infection
• Azithromycin 1 g single oral dose
Refer urgently for surgical opinion
• Reassure patient and educate
• Provide analgesics, if necessary
• Promote and provide condoms
• Offer HIV Counseling and Testing.
1. Counsel on risk reduction
2. Promote and provide condoms
3. Offer HIV Counseling and Testing
4. Manage and treat Partner
5. Review in 7 days or earlier, if necessary, if worse refer


6. LOWER ABDOMINAL PAIN
Patient complains of lower abdominal pain
Take history and conduct abdominal and vaginal examination
Any of the following present?
• Missed/overdue periods
• Recent delivery, abortion or miscarriage
• Abdominal guarding and/or rebound tenderness
• Abnormal vaginal bleeding
• Abdominal mass
No
Yes
1. Set up an IV line and apply resuscitatory measures if necessary
2. Refer for surgical and gynaecological opinion and assessment
Lower abdominal tenderness?
No
Yes
Any vaginal discharge?
No
Yes
Follow vaginal discharge flow chart
Any other illnesses?
No
Yes
Manage appropri-ately
1. Counsel on risk reduction
2. Promote and provide condoms
3. Offer HIV Counseling and Testing
Refer to higher level care for Rx which includes:
1.Cefixime 400mg single dose
2. • Azithromycine 1 g single dose OR
• Doxycycline 100mg x 2/day x 14 days
3.Metronidazole 500mg x 2 /day for 14 days
4. Review in 3 days
1. Continue treatment until completed
2. Counsel on risk reduction
3. Promote and provide con-doms
4. Offer HIV Counseling and Testing
5. Ask patient to return if necessary
Has the patient improved?
• Absence of fever
• Reduction in abdominal tenderness
No
REFER
Yes


7. NEONATAL CONJUNCTIVITIS
(Ophthalmia neonatorum)
Neonate with eye discharge
Take history and examine
Bilateral or unilateral swollen eyelids and purulent discharge?
No
yes
• Reassure mother
• Advise return, if necessary
1. Treat for gonococcal infection
• Cefixime, oral suspension, 8mg/kg body wt., single dose
2. Treat for chlamydia infection
• Azithromycin,suspension, 200 mg/5ml, give 10mg/kg body wt. single dose
3. Treat mother and her sexual partner(s) for gonorrhoea and chlamydia (see flowchart for vaginal discharge)
1. Educate mother
2. Counsel mother
3. Advise to return on the 3rd day
Improved?
No
Yes
REFER
1. Reassure mother
2. Continue treatment for 14 days
3. Educate mother
4. Counsel mother

HEPATITIS B (ENVELOPED DNA VIRUS)

- Common, Endemic in much of Asia and the Far East
- *National -wide prevalence* 6.5% (5/2015, Dept of Medical Research and Dept. of Public Health)
- The virus has 3 major structural antigens: HBsAg, HBcAg, HBeAg. Spread is via infected blood, sexual intercourse, from mother to newborn baby, or via human bites.
- *Incubation period* is 6- 23 weeks (average l 7weeks)
- HBV infection can be either acute or chronic and the associated illness ranges in severity from asymptomic to symptomic, progressive disease (cirrhosis, HCC).
- Antiviral agents active against HBV are available, and have been shown to suppress HBV replication, prevent to progression cirrhosis and reduce the risk of HCC and liver related deaths.
- However, currently available treatments fail to eradicate the virus in most of those treated, necessitating potentially lifelong treatment.



Summary of recommendations for persons with chronic hepatitis B infection

Non-invasive assessment of liver disease stage at baseline and during follow up

	APRI (aspartate aminotransferase [AST] to-platelet ratio index) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. Transient elastography (e.g. Fibro Scan) or Fibro Test may be the preferred NITs in settings where they are available and cost is not a major constraint. (Conditional recommendation, low quality of evidence)

Who to treat and who not to treat in persons with chronic hepatitis B

Who to treat	*As a priority, all adults, adolescents and children with CHB and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels. (strong recommendation, moderate quality of evidence)* *Treatment is recommended for adults with CHB who do not have clinical evidence of cirrhosis (or based on APRI score: SI in adults), but are aged more than 30 years (in particular), and have persistently abnormal ALT levels and evidence of high-level HBV replication (HBV DNA >20 000 IU/L), regardless of HBeAg status. (strong recommendation, moderate quality of evidence)* *Where HBV DNA testing is not available. Treatment may be considered based on persistently abnormal ALT levels alone, regardless of HBeAg status. (Conditional recommendation, low quality of evidence).*
Existing recommendation for HBV/HIV-coinfected persons	*In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART. (Strong recommendation, moderate quality of evidence)* *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach.*

Second-line antiviral therapies for the management of treatment failure

	In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, a switch to tenofovir 300 mg od is recommended. (Strong recommendation, low quality of evidence)

When to stop treatment

Lifelong NA therapy	*All persons **with cirrhosis** based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with nucleos(t)ide analoges (NAs), and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury. (Strong recommendation, low quality of evidence)*
Discontinuation	*All persons **with cirrhosis** based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with nucleos(t)ide*

	analoges (NAs), and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury. (Strong recommendation, low quality of evidence)
Discontinuation	*Discontinuation of NA therapy may be considered exceptionally in:* *Persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults);* ***And** who can be followed carefully long term for reactivation;* ***And** if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg positive) and after completion of at least one additional year of treatment;* ***And** in association with persistently normal ALT levels **and** persistently undetectable HBV DNA levels (where HBV DNA testing is available).* *Where HBV DNA testing is not available: Discontinuation of NA therapy may be considered in persons who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of prior HBeAg status. (Conditional recommendation, low quality of evidence)*
Retreatment	*Relapse may occur after stopping therapy with NAs. Retreatment is recommended if there are consistent signs of reactivation (HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again) (where HBV DNA testing is available). (Strong recommendation, low quality of evidence)*

Monitoring

Monitoring for disease progression and treatment response in persons with CHB prior to, during and post-treatment	
	It is recommended that the following be monitored at least annually: *ALT level (and AST for APRI), HBsAg, HBeAg, and HBV DNA levels (where HBV DNA testing is available)* *Non-invasive tests (APRI score or Fibro scan) to assess for the presence of cirrhosis, in those without cirrhosis at baseline;* *If on treatment, adherence should be monitored regularly and at each visit.* *(Strong recommendation, moderate quality of evidence)*
More frequent monitoring	*In persons who do not yet meet the criteria for antiviral therapy: more frequent monitoring for disease progression may be indicated in: persons who have intermittently abnormal ALT levels or HBV DBA levels that fluctuate between 2,000 - 20,000 IU/ml (where HBV DNA testing is available), and in HIV-*

	coinfected persons, (Conditional recommendation, low quality of evidence) *In persons on treatment or following treatment discontinuation: More frequent on-treatment monitoring (at least every 3 months for the first year) is indicated in: persons with more advanced disease (compensated or decompensated cirrhosis): during the first year of treatment to assess treatment response and adherence; where treatment adherence is a concern; in HIV-coinfected persons; and in persons after discontinuation of a treatment. (Conditional recommendation, very low quality of evidence)*

Monitoring for tenofovir and entecavir toxicity

	Measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered in all persons prior to initation of antiviral therapy. *Renal function should be monitored annually in persons on long-term tenofovir or entecavir therapy, and growth monitored carefully in children. (Conditional recommendation, very low quality of evidence)*

Monitoring for hepatocellular carcinoma

	Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein (AFP) testing every six months is recommended for: • *Persons with cirrhosis, regardless of age or other risk factors (strong recommendation, low quality of evidence)* • *Persons with a family history of HCC (Strong recommendation, low quality of evidence)* • *Persons aged over 40 years (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on APRI score ::::2),and with HBV DNA level >2000 IU/ml (where HBV DNA testing is available). (Conditional recommendation, low quality of evidence)*

Prevention

Infant and neonatal hepatitis B vaccination	
Existing recommendations in infants and neonates[1]	*All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three* *doses.*

	[1]WHO. Hep atitis B vaccines. Wkly Epid emiol Rec. 2009;84:405-20.

Prevention of mother-to-child HBV transmission using antiviral therapy

	In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults, and tenofovir is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission.
Existing recommendations in HIV-infected pregnant and breastfeeding women	*In HIV-infected pregnant and breastfeeding women (including pregnant women in the first trimester of pregnancy and women of childbearing age), a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as first-line ART. This recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped. (Strong recommendation, low to moderate quality of evidence)* [2]*Consolidated guidelines on the use of antiretroviral drugsfor treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.*

Prevention

- WHO recommends implementation of blood safety strategies and safer sex practices, including minimizing the number of partners and using barrier protective measures (condoms), also protect against transmission.

Management of Persons Who Are HBsAg Positive

Recommendations for management of all persons with HBsAg include the following:

- To verify the presence of chronic HBV infection, persons with HBsAg should be retested.
- The absence of IgM anti-HBc or the persistence of HBsAg for ≥6 months indicates chronic HBV infection.
- Persons with chronic HBV infection should be referred for evaluation to a specialist experienced in managing chronic hepatitis B infection.
- Household, sexual, and needle-sharing contacts of persons with chronic infection should be evaluated. Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing (see Prevaccination Serologic Testing).
- Susceptible persons should complete the vaccine series by using an age-appropriate vaccine dose and schedule.
- Sex partners of persons with HBsAg should be counseled to use latex condoms to protect themselves from sexual exposure to infectious body fluids (e.g., semen and vaginal secretions), unless they have been demonstrated to be immune after vaccination (anti-HBs ≥10 mIU/mL) or previously infected (anti-HBc positive).

To prevent or reduce the risk for transmission to others in addition to vaccination,

- persons with HBsAg also should be advised to use methods (e.g., condoms) to protect nonimmune sex partners from acquiring HBV infection from sexual activity until the partner can be vaccinated and immunity documented;
- cover cuts and skin lesions to prevent spread by infectious secretions or blood;
- refrain from donating blood, plasma, body organs, other tissue, or semen;
- and refrain from sharing household articles (e.g., toothbrushes, razors, or personal injecting equipment) that could become contaminated with blood, and refrain from premastication of food.

To protect the liver from further harm, persons with HBsAg should be advised

- to avoid or limit alcohol consumption because of the effects of alcohol on the liver;
- refrain from starting any new medicines, including over-the-counter and herbal medicines, without checking with their health care provider; and obtain vaccination against hepatitis A.

When seeking medical or dental care, persons who are HBsAg positive should be advised

- to inform their health care providers of their HBsAg status so that they can be evaluated and managed.

The following are key counseling messages for persons with HBsAg:

- HBV is not usually spread by hugging, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact.
- Persons should not be excluded from work, school, play, childcare, or other settings because they are infected with HBV.
- Involvement with a support group might help patients cope with chronic HBV infection.
- HBV infection is a chronic condition that can be treated, and patients should receive prevention counseling and be evaluated for antiviral treatment.

Special Considerations

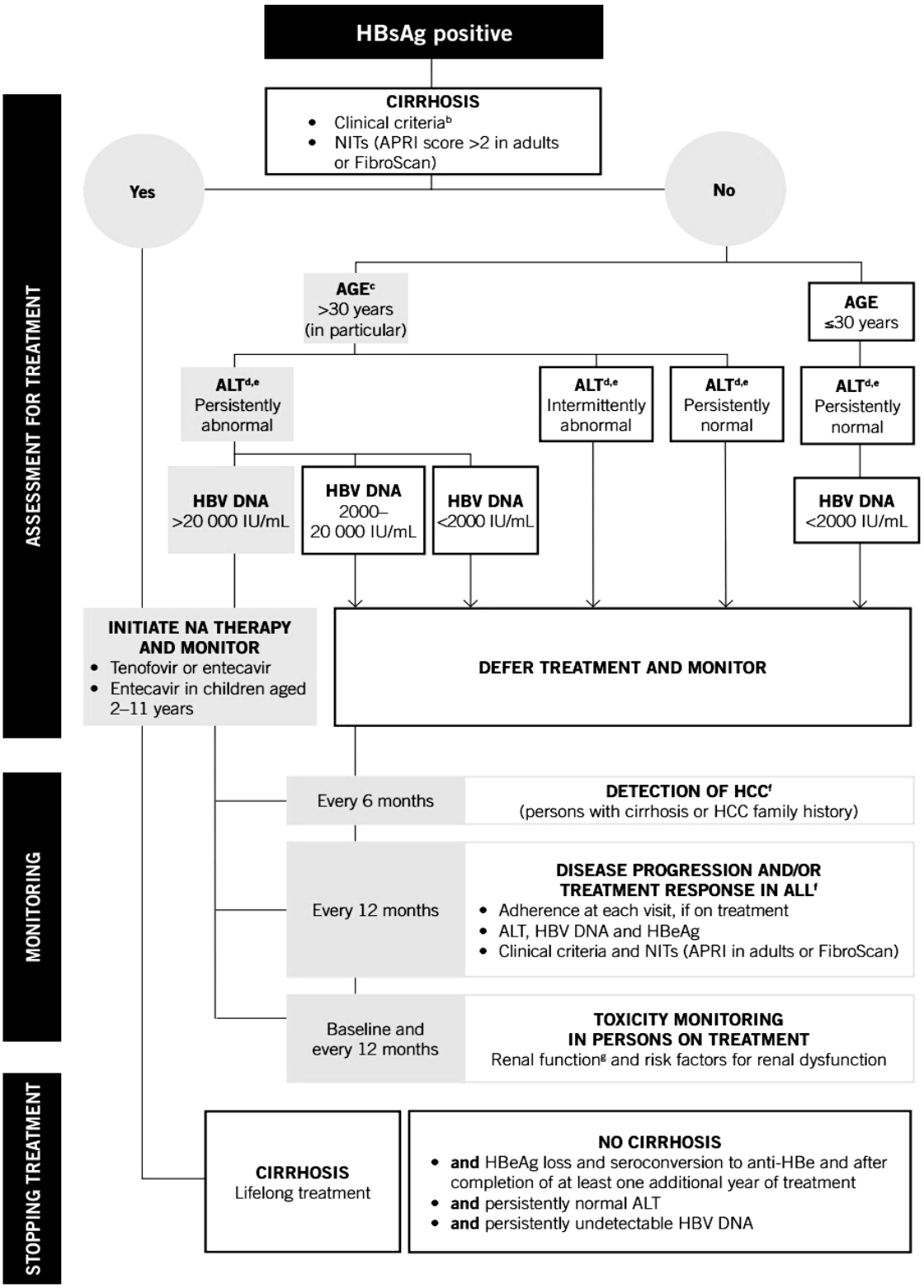
Pregnancy

- Regardless of whether they have been previously tested or vaccinated, all pregnant women should be tested for HBsAg at the first prenatal visit and again at delivery if at high risk for HBV infection. Pregnant women at risk for HBV infection and without documentation of a complete hepatitis B vaccine series should receive hepatitis B vaccination.

HIV Infection

- HIV infection can impair the response to hepatitis B vaccination. Persons with HIV should be tested for anti-HBs 1–2 months after the third vaccine dose .Modified dosing regimens, including a doubling of the standard antigen dose and administration of additional doses, might increase the response rate and should be managed in consultation with an infectious disease specialist

ALGORITHM OF WHO RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a]



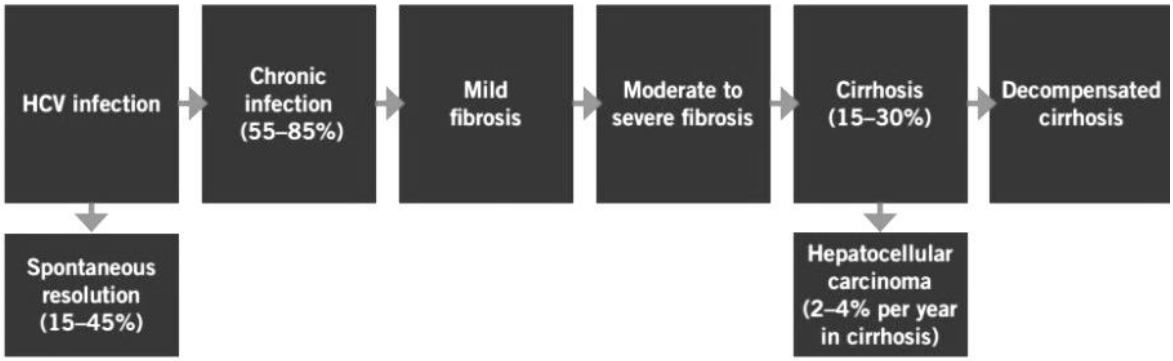
Reference

5. *WHO Treatment Guideline of Hepatitis B*
6. *https://www.who.int/news-room/fact-sheets/detail/hepatitis-b*
7. *https://www.cdc.gov/std/treatment-guidelines/hbv.htm*

HEPATITIS C (RNA VIRUS)

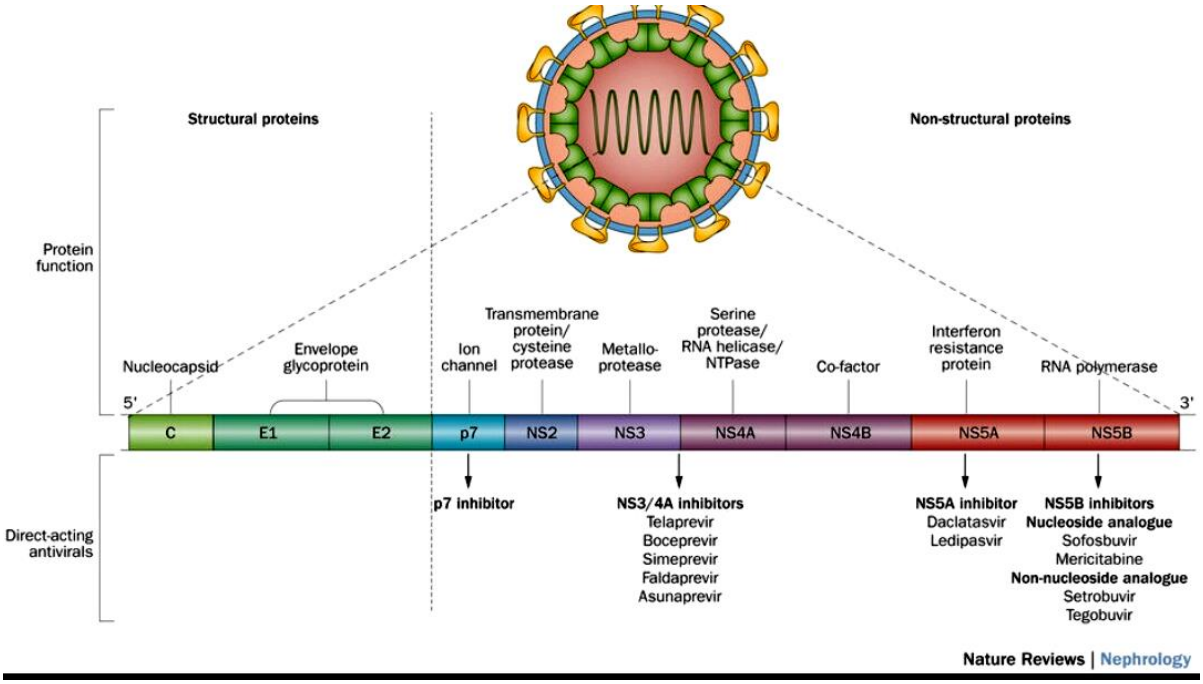
- HCV is a major cause of acute and chronic hepatitis.
- National wide prevalence survey HCV -2.7% (Dept of Medical research and Dept of public health 5/2015)
- Should be tested anybody attending clinic for any illness or patient's desire.

Natural history of HCV



Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and HCC (Fig. 2.2). Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years *(71–73)*. The risk of HCC in persons with cirrhosis is approximately 2–4% per year *(74)*.

- Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and HCC (Fig. 2.2). Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15-30% within 20 years *(71-73)*. The risk of HCC in persons with cirrhosis is approximately 2-4% per year *(74)*.
- Anti HCV antibody testing can be done by ICT or ELISA. ICT testing needs confirmation by ELISA.
- HCV RNA assay via PCR-quantitative for HCV genome.
- HCV genotyping is necessary for treatment option.



Management

- To clear HCV (not anti-HCV Ab, will persist for life)

Prioritization of HCV patients

- Patients with compensated cirrhosis
- With co-infections (HIV, HBV)
- Fibrosis stage F3 and F4
- Pretreatment assessment
- Alcohol consumption
- Exclusion of HCC
- HIV status, current ART treatment
- Pregnancy status (contraception during /after 6 months)
- Baseline biochemical test
- U&E, creatinine
- FBC
- Fetoprotein
- Fibroscan
- Direct acting antivirals (DAAs)
- Protease inhibitors (PI), Nucleotide inhibitor (NI), Non nucleotide inhibitor (NNI), NS5B inhibitors

Recommended regimens

- Sofosbuvir + Rabavrin *24week (for all genotypes)
- If Daclatasvir is available, Sofosbuvir + Daclatasvir * 2 wk (for all genotypes)
- If ledipasvir is available Sofosbuvir+ Ledipasvir* 12wk (for genotype 1& 6)
- 24weeks (for cirrhotic patients and Genotype 2,3,4 & 6)

Dosage

- **Oral Rabavirin** 200mg capsule /tab.
    - Body Wt. <75kg-2(morning),3 (evening)
- **Sofosbuvir**
- **Dacastasvir/Sofosbuvir Ledipsvir/Sofosbuvir**
    - >75kg-3(morning),3(evening) 400mg once daily(morning)
    - (30 or 60mg/ 400mg) once daily- morning (90 mg/400mg) once daily-morning
- The dose of daclatavir should be reduced to 30mg with the antibiotics (clarithromycin, erythromycin, ketoconazole, itraconazole)

Treatment monitoring

On treatment monitoring, baseline biochemical test may be necessary.

Post treatment Biochemical tests

- LFT, renal function (ALT, AST, Alkaline phosphate, bilirubin, Urea and creatinine) <3monthly>
- Alpha fetoprotein and USG .....<6monthly>

Post treatment assessment is done at 12wks after the termination of the treatment by viral load testing (SVR 12)

Patients who achieved SVR still needs to be followed -up regularly for the assessment of cirrhosis status and for the surveillance of HCC.

Those patients who do not receive treatment or treated and do not achieve SVR should also be followed-up.

Monitoring of drug side effects

Sofosbuvir

- The side effects of Sofosbuvir are fatigue, nausea, rash, itching, irritability, decreased appetite and diarrhea.

Supportive treatments

- Renal function should be checked regularly

Ribavirin containing regimen

- Mild anemia
- Significant teratogenic and/or embryocidal effects.
- Women of childbearing potential and/or their male partners must use an effective form of contraception during treatment and for a period of six months after the treatment has concluded.

Ribavirin should not be co-administered with Didanosine and Zidovudine. (WHO guideline 2014)

Daclatasvir

- The most common adverse reactions related to this drug are fatigue, headache and nausea.

Sofosbuvir and Ledipasvir

- In clinical studies, fatigue and headache were more common in patients treated with Sofosbuvir and Ledipasvir compared to placebo.

Prevention

Measures to avoid transmission of HCV

- HCV infected persons should be counseled to avoid sharing tooth brushes and dental or shaving equipment, and be cautioned to cover any bleeding wound in order to prevent contact of their blood with others.
- Persons should be counseled to stop using illicit drugs. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water. Cotton or other paraphernalia.
- Persons with HCV infection should be provided information about how to protect their liver from further harm (i.e., hepatotoxic agents); for instance, persons with HCV infection should be advised to avoid drinking alcohol and taking any new medicines, including over-the-counter or herbal medications, without checking with their clinician.
- In addition, a need for hepatitis A and B vaccination should be determined; persons who are not immune should be vaccinated.
- HCV infected persons should be advised not to donate blood, body organs, other tissue or semen.
- HCV infected person should be counseled that the risk of sexual transmission is low, and that the infection itself is not a reason to change sexual practices (i.e, those in long term relationships need not start using barrier precautions, and others should always practice "safer" sex).

Primary prevention interventions recommended by WHO include:

- safe and appropriate use of health care injections;
- safe handling and disposal of sharps and waste;
- provision of comprehensive harm-reduction services to people who inject drugs;
- testing of donated blood for HBV and HCV (as well as HIV and syphilis);
- training of health personnel; and
- prevention of exposure to blood during sex.

Special Considerations

Pregnancy

- All pregnant women should be screened with each pregnancy for HCV antibodies at the first prenatal visit in settings where the HCV prevalence is >0.1%. HCV has not been reported to be transmitted through breast milk, although mothers with HCV infection should consider abstaining from breastfeeding if their nipples are cracked or bleeding

HIV Infection

- All persons with HIV infection should undergo serologic screening for HCV at initial evaluation.
- Acute HCV infection acquisition among persons with HIV infection can occur, especially among MSM, and regular screening of those with HIV is cost-effective.
- Antibody to HCV remains positive after spontaneously resolved infection or successful treatment; therefore, subsequent testing for potential HCV reinfection among persons with ongoing risk should be limited to HCV RNA testing only.
- Because a minimal percentage of persons with HIV infection do not develop HCV antibodies, HCV RNA testing should be performed for persons with HIV infection and unexplained liver disease who are anti-HCV negative.
- The course of liver disease is more rapid among persons with HIV and HCV, and the risk for cirrhosis is higher than that for persons with HCV infection alone.

Reference

1. *Therapeutic Manual, Internal Medicine, MMA, 1'1 Edition*
2. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c (24 June 2022-WHO)
3. https://www.cdc.gov/std/treatment-guidelines/hbv.htm

OVERVIEW OF COVID-19

- *The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of January 10, 2023, more than 600 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 6 million deaths. In Myanmar, the first COVID 19 case was detected on 23.3.2020.*
- *Individuals of all ages are at risk for SARS-CoV-2 infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions.*
- *In an analysis of more than 1.3 million laboratory-confirmed cases of COVID-19 that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died.*
- *The percentage of patients who died was 12 times higher among those with reported medical conditions (19.5%) than among those without medical conditions (1.6%), and the percentage of patients who were hospitalized was 6 times higher among those with reported medical conditions (45.4%) than among those without medical conditions (7.6%).*
- *Mortality was highest in patients aged >70 years, regardless of the presence of chronic medical conditions. Data on co morbid health conditions among patients with COVID-19 indicate that 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease.*
- *Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, liver disease (especially in patients with cirrhosis), obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19.*

SARS-CoV-2 Variants

- *Like other RNA viruses, SARS-CoV-2 is constantly evolving through random mutations. New mutations can potentially increase or decrease infectiousness and virulence. In addition, mutations can increase the virus' ability to evade adaptive immune responses from past SARS-CoV-2 infection or vaccination.*
- *This viral evolution may increase the risk of reinfection or decrease the efficacy of vaccines. There is evidence that some SARS-CoV-2 variants have reduced susceptibility to plasma from people who were previously infected or immunized, as well as to certain monoclonal antibodies (mAbs) that are being considered for prevention and treatment.*

- *Since December 2020, the World Health Organization (WHO) has assigned Greek letter designations to several identified variants.*
- *The Omicron (B.1.1.529) variant was designated a VOC in November 2021 and rapidly became the dominant variant across the globe. More recently, the Omicron subvariants BA.1, BA.1.1, and BA.2 have emerged. The Omicron VOC is more transmissible than other variants and is not susceptible to some of the anti-SARS-CoV-2 mAbs that have been developed for treatment and prevention.*
- *The Omicron VOC has surpassed Delta (B.1.617.2) as the dominant variant in the United States; the Delta variant was first identified in India and was the dominant variant in July 2021. Up to date , the dominant variants are BQ.1.1 and XBB 1.5 which are sub variants of omicron.*

Clinical Presentation

- *The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.*
- *The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Among 72,314 people with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnoea, respiratory frequency ≥30 breaths/min, oxygen saturation ≤93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO2/FiO2] <300 mm Hg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiple organ dysfunction syndrome or failure).*
- *In a report on more than 370,000 confirmed COVID-19 cases with reported symptoms in the United States, 70% of patients experienced fever, cough, or shortness of breath; 36% had muscle aches; and 34% reported headaches.*
- *Other reported symptoms have included, but are not limited to, diarrhoea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting. The abnormalities seen in chest X-rays of patients with COVID-19 vary, but bilateral multifocal opacities are the most common.*
- *The abnormalities seen in computed tomography of the chest also vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course of COVID-19.31 Imaging may be normal early in infection and can be abnormal in the absence of symptoms.*
- *Common laboratory findings in patients with COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevated levels of aminotransferase, C-reactive protein, D-dimer, ferritin, and*

lactate dehydrogenase.

- *Although COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac, dermatologic,hematologic,hepatic, neurologic, renal, and other complications.*
- *Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients. The long-term sequelae of COVID-19 survivors are currently unknown.*
- *Persistent symptoms after recovery from acute COVID-19 have been described . Lastly, SARS-CoV-2 infection has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children, or MIS-C).*

Clinical Spectrum of SARS-CoV-2 Infection

- *Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories; however, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient's clinical status may change over time.*
- *Asymptomatic or presymptomatic infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19.*
- *Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging. •*
- *Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥94% on room air at sea level.*
- *Severe illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.*
- *Critical illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunctions. Infectious complications in patients with COVID-19 can be categorized as follows:*
- *Coinfections at presentation: Although most individuals present with only SARS-CoV-2 infection, concomitant viral infections, including influenza and other respiratory viruses, have been reported. Community-acquired bacterial pneumonia has also been reported, but it is uncommon, with a prevalence that ranges from 0% to 6% of people with SARS-CoV-2 infection Antibacterial therapy is generally not recommended unless additional*

evidence for bacterial pneumonia is present (e.g., leukocytosis, the presence of a focal infiltrate on imaging).

- *Reactivation of latent infections: There are case reports of underlying chronic hepatitis B virus and latent tuberculosis infections reactivating in patients with COVID-19 who receive immunomodulators as treatment, although the data are currently limited.*
- *Reactivation of herpes simplex virus and varicella zoster virus infections have also been reported. Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.*
- *Many clinicians would initiate empiric treatment (e.g., with the antiparasitic drug ivermectin), with or without serologic testing, in patients who are from areas where Strongyloides is endemic (i.e., tropical, subtropical, or warm temperate areas). •*
- *Nosocomial infections: Hospitalized patients with COVID-19 may acquire common nosocomial infections, such as hospital-acquired pneumonia (including ventilator-associated pneumonia), line-related bacteremia or fungemia, catheter-associated urinary tract infection, and Clostridioides difficile–associated diarrhea. Early diagnosis and treatment of these infections are important for improving outcomes in these patients. •*
- *Opportunistic fungal infections: Invasive fungal infections, including aspergillosis and mucormycosis, have been reported in hospitalized patients with COVID-19. Although these infections are relatively rare, they can be fatal, and they may be seen more commonly in patients who are immunocompromised or receiving mechanical ventilation. The majority of mucormycosis cases have been reported in India and are associated with diabetes mellitus or the use of corticosteroids.The approach for managing these fungal infections should be the same as the approach for managing invasive fungal infections in other settings.*

Persistent Symptoms and Other Conditions after Acute COVID-19 (Post Covid Syndrome)

- *Some patients may experience persistent symptoms or other conditions after acute COVID-19. Adult and pediatric data on the incidence, natural history, and etiology of these symptoms and organ dysfunction are emerging.*
- *However, reports on these data have several limitations, including differing case definitions. In addition, many reports only included patients who attended post-COVID-19 clinics, and the studies often lack comparator groups. No specific treatments for persistent effects of COVID-19 have been shown to be effective, although general management strategies have been proposed.*
- *The CDC has defined post-COVID-19 conditions as new, returning, or*

ongoing symptoms that people experience ≥4 weeks after being infected with SARS-CoV-2. In October 2021, the World Health Organization published a clinical case definition that described the post-COVID-19 clinical condition as usually occurring 3 months after the onset of COVID-19 with symptoms that last for ≥2 months and cannot be explained by an alternative diagnosis.

Clinical Management of Adults Summary

- *Two main processes are thought to drive the pathogenesis of COVID-19.*
- *Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2.*
- *Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.*

Table 2a. Therapeutic Management of Nonhospitalized Adults With COVID-19

Patient Disposition	Panel's Recommendations
Does Not Require Hospitalization or Supplemental Oxygen	**For All Patients:** • All patients should be offered symptomatic management **(AIII)**. • The Panel **recommends against** the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication **(AIIb)**. **For Patients Who Are at High Risk of Progressing to Severe COVID-19**[b] *Preferred Therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative Therapies. For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order* • **Bebtelovimab**[f] **(CIII)** • **Molnupiravir**[d,g] **(CIIa)**
Discharged from Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone**[a] **(AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged from Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but still require oxygen*[h]	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged from ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[i]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not exceed** 10 days) with careful monitoring for AEs **(BIII)**. Because remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[j] clinicians may consider using it in this setting. As remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion	

[a] There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in this setting may cause harm.

[b] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19.

[c] Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

[d] If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.

[e] Administration of remdesivir requires 3 consecutive days of IV infusion.

[f] Bebtelovimab is active in vitro against all circulating Omicron (B.1.1.529) subvariants, but there are no clinical efficacy data from placebo-controlled trials that evaluated the use of bebtelovimab in patients who are at high risk of progressing to severe COVID-19. Therefore, bebtelovimab should be used only when the preferred treatment options are not available, feasible to use, or clinically appropriate.

[g] Molnupiravir has lower efficacy than the preferred treatment options. Therefore, it should be used only when the

- *COVID-19 Treatment Guidelines* 47

preferred options are not available, feasible to use, or clinically appropriate.

[h] These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

[i] Provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen for the first time or are increasing their baseline oxygen requirements), pulse oximetry, laboratory monitoring, and close follow-up through telehealth, visiting nurse services, or in-person visits.

- # General Management of Nonhospitalized Patients With Acute COVID-19

Last Updated: December 16, 2021

Summary Recommendations
• Management of nonhospitalized patients with acute COVID-19 should include providing supportive care, considerir the use of COVID-19-specific therapy for patients who have a high risk for disease progression, taking steps to red the risk of SARS-CoV-2 transmission (including isolating the patient), and advising patients on when to contact a health care provider and seek an in-person evaluation **(AIII)**.
• When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether tl require COVID-19-specific therapy and in-person care **(AIII)**.
• Patients with dyspnea should be referred for an in-person evaluation by a health care provider and should be follow closely during the initial days after the onset of dyspnea to assess for worsening respiratory status **(AIII)**.
• Management plans should be based on a patient's vital signs, physical exam findings, risk factors for progression t severe illness, and the availability of health care resources **(AIII)**.
• See Therapeutic Management of Nonhospitalized Adults With COVID-19 for specific recommendations on using pharmacologic therapy in nonhospitalized patients.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opini

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Managing Patients with COVID-19 in an Ambulatory Care Setting

- *Approximately 80% of patients with COVID-19 have mild illness that does not warrant medical intervention or hospitalization. Most patients with mild COVID-19 (defined as the absence of viral pneumonia and hypoxemia) can be managed in an ambulatory care setting or at home.*
- *Patients with moderate COVID-19 (those with viral pneumonia but without hypoxemia) or severe COVID-19 (those with dyspnea, hypoxemia, or lung infiltrates >50%) need in-person evaluation and close monitoring, as pulmonary disease can progress rapidly and require hospitalization.*
- *Health care providers should identify patients who may be at high risk for*

progression to severe COVID-19; these patients may be candidates for anti-SARS-CoV-2 monoclonal antibody treatment.. When managing outpatients with COVID-19, clinicians should provide supportive care, take steps to reduce the risk of SARS-CoV-2 transmission (e.g., wear a mask, isolate the patient),4,5 evaluate the need for COVID-19- specific therapy, and advise patients on when to seek in-person evaluation.6 Supportive care includes managing symptoms (as described below), ensuring that patients are receiving the proper nutrition, and paying attention to the risks of social isolation, particularly in older adults.

- *Other unique aspects of care for geriatric patients with COVID-19 include considerations related to cognitive impairment, frailty, fall risk, and polypharmacy. Older patients and those with chronic medical conditions have a higher risk for hospitalization and death; however, SARS-CoV-2 infection may cause severe disease and death in patients of any age, even in the absence of any risk factors. The decision to monitor a patient in the outpatient setting should be made on a case-by-case basis.*
- *Assessing the Need for In-Person Evaluation When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care (AIII).*
- *Outpatient management may include the use of patient self-assessment tools. During initial triage, clinic staff should determine which patients are eligible to receive supportive care at home and which patients warrant an in-person evaluation.8 Local emergency medical services, if called by the patient, may also be of help in deciding whether an in-person evaluation is indicated. Patient management plans should be based on the patient's vital signs, physical exam findings, risk factors for progression to severe illness, and the availability of health care resources (AIII).*
- *All patients with dyspnea, oxygen saturation (SpO2) ≤94% on room air at sea level (if this information is available), or symptoms that suggest higher acuity (e.g., chest pain or tightness, dizziness, confusion or other mental status changes) should be referred for an in-person evaluation by a health care provider (AIII).*
- *The criteria used to determine the appropriate clinical setting for an in-person evaluation may vary by location and institution; it may also change over time as new data and treatment options emerge. There should be a low threshold for in-person evaluation of older persons and those with medical conditions that are associated with a risk of progression to severe COVID-19. The individual who performs the initial triage should use their clinical judgement to determine whether a patient requires ambulance transport.*
- *There are unique considerations for residents of nursing homes and other long-term care facilities who develop acute COVID-19. Decisions about transferring these patients for an in-person evaluation should be a*

collaborative effort between the resident (or their health care decision maker), a hospital-based specialist (e.g., an emergency physician or geriatrician), and the clinical manager of the facility.

- *In some settings where clinical evaluation is challenged by geography, health care provider home visits may be used to evaluate patients.10 Patients who are homeless should be provided with housing where they can adequately self-isolate. Providers should be aware of the potential adverse effects of prolonged social isolation, including depression and anxiety. All outpatients should receive instructions regarding self-care, isolation, and follow-up, and should be advised to contact a health care provider or a local ED for any worsening symptoms.*
- *Clinical Considerations When Managing Patients in an Ambulatory Care Setting Persons who have symptoms that are compatible with COVID-19 should undergo diagnostic SARS-CoV-2 testing (see Prevention of SARS-CoV-2 Infection). Patients with SARS-CoV-2 infection may be asymptomatic or experience symptoms that are indistinguishable from other acute viral or bacterial infections (e.g., fever, cough, sore throat, malaise, muscle pain, headache, gastrointestinal symptoms).*
- *It is important to consider other possible etiologies of symptoms, including other respiratory viral infections (e.g., influenza), community-acquired pneumonia, congestive heart failure, asthma or chronic obstructive pulmonary disease exacerbations, and streptococcal pharyngitis. In most adult patients, if dyspnea develops, it tends to occur between 4 and 8 days after symptom onset, although it can also occur after 10 days.13 While mild dyspnea is common, worsening dyspnea and severe chest pain/tightness suggest the development or progression of pulmonary involvement.*
- *In studies of patients who developed acute respiratory distress syndrome, progression occurred a median of 2.5 days after the onset of dyspnea.14-16 Adult outpatients with dyspnea should be followed closely with telehealth or in-person monitoring, particularly during the first few days following the onset of dyspnea, to monitor for worsening respiratory status (AIII). If an adult patient has access to a pulse oximeter at home, SpO2 measurements can be used to help assess overall clinical status.*
- *Patients should be advised to use pulse oximeters on warm fingers rather than cold fingers for better accuracy. Patients should inform their health care provider if the value is repeatedly below 95% on room air at sea level. Pulse oximetry may not accurately detect occult hypoxemia, especially in Black patients. Additionally, SpO2 readings obtained through a mobile phone application may not be accurate enough for clinical use. Importantly, oximetry should only be interpreted within the context of a patient's entire clinical presentation (i.e., results should be disregarded if a patient is complaining of increasing dyspnea).*

Counseling Regarding the Need for Follow-Up

- *Health care providers should identify patients who are at high risk for disease progression. These patients may be candidates for anti-SARS-CoV-2 monoclonal antibody treatments, and clinicians should ensure that these patients receive adequate medical follow-up. The frequency and duration of follow-up will depend on the risk for severe disease, the severity of symptoms, and the patient's ability to self-report worsening symptoms.*
- *Health care providers should determine whether a patient has access to a phone, computer, or tablet for telehealth; whether they have adequate transportation for clinic visits; and whether they have regular access to food. The clinician should also confirm that the patient has a caregiver who can assist with daily activities if needed. All patients and/or their family members or caregivers should be counseled about the warning symptoms that should prompt re-evaluation through a telehealth visit or an in-person evaluation in an ambulatory care setting or ED.*
- *These symptoms include new onset of dyspnea; worsening dyspnea (particularly if dyspnea occurs while resting or if it interferes with daily activities); dizziness; and mental status changes, such as confusion. Patients should be educated about the time course of these symptoms and the possible respiratory decline that may occur, on average, 1 week after the onset of illness.*

Managing Adults With COVID-19 Following Discharge from the Emergency Department

- *There are no fixed criteria for admitting patients with COVID-19 to the hospital; criteria may vary by region and hospital facilities. Patients with severe disease are typically admitted to the hospital, but some patients with severe disease may not be admitted due to a high prevalence of infection and limited hospital resources. In addition, patients who could receive appropriate care at home but are unable to be adequately managed in their usual residential setting are candidates for temporary shelter in supervised facilities, such as a COVID-19 alternative care facility.*
- *For example, patients who are living in multigenerational households or who are homeless may not be able to self-isolate and should be provided resources such as dedicated housing units or hotel rooms, when available. Unfortunately, dedicated residential care facilities for COVID-19 patients are not widely available, and community-based solutions for self-care and isolation should be explored.*
- *In the cases where institutional resources (e.g., inpatient beds, staff members) are scarce, it may be necessary to discharge an adult patient and provide an advanced level of home care, including supplemental oxygen (if indicated), pulse oximetry, and close follow-up. Although early discharge of those with severe disease is not generally recommended by*

the Panel, it is recognized that these management strategies are sometimes necessary. In these situations, some institutions are providing frequent telemedicine follow-up visits for these patients or providing a hotline that allows patients to speak with a clinician when necessary.

- *Home resources should be assessed before a patient is discharged from the ED; outpatients should have a caregiver and access to a device that is suitable for telehealth. Patients and/or their family members or caregivers should be counseled about the warning symptoms that should prompt re-evaluation by a health care provider. Special consideration may be given to using certain therapeutics (e.g., dexamethasone) in this setting.*

Managing Adults With COVID-19 Following Hospital Discharge

- *Most patients who are discharged from the hospital setting should have a follow-up visit with a health care provider soon after discharge. Whether an in-person or a telehealth visit is most appropriate depends on the clinical and social situation. In some cases, adult patients are deemed to be stable for discharge from the inpatient setting even though they still require supplemental oxygen. Special consideration may be given to using certain therapeutics (e.g., dexamethasone) in this setting. When possible, these individuals should receive oximetry monitoring and close follow-up through telehealth visits, visiting nurse services, or in-person clinic visits.*
- *Considerations in Pregnancy Managing pregnant outpatients with COVID-19 is similar to managing nonpregnant patients .*
- *In pregnant patients, SpO2 should be maintained at 95% or above on room air at sea level; therefore, the threshold for monitoring pregnant patients in an inpatient setting may be lower than in nonpregnant patients.*
- *In general, there are no changes to fetal monitoring recommendations in the outpatient setting, and fetal management should be similar to the fetal management used for other pregnant patients with medical illness. However, these monitoring strategies can be discussed on a case-by-case basis with an obstetrician. Pregnant and lactating patients should be given the opportunity to participate in clinical trials of outpatients with COVID-19 to help inform decision-making in this population.*

Considerations in Children

- *Children and adolescents with acute COVID-19 are less likely than adults to require medical intervention or hospitalization, and most can be managed in an ambulatory care setting or at home. In general, the need for ED evaluation or hospitalization should be based on the patient's vital signs, physical exam findings (e.g., dyspnea), and risk factors for progression to severe illness. Certain groups, including young infants, children with risk factors, and those with presentations that overlap with multisystem inflammatory syndrome in children (MIS-C), may require*

hospitalization for more intensive monitoring.

- *However, this should be determined on a case-by-case basis. Most children with mild or moderate COVID-19, even those with risk factors, will not progress to more severe illness and will recover without specific therapy. There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products in nonhospitalized children with COVID-19 who have risk factors for severe disease.*
- *The available efficacy data for adults suggests that anti-SARS-CoV-2 monoclonal antibody products may be considered for use in children who meet the Food and Drug Administration Emergency Use Authorization (EUA) criteria, especially those who have more than 1 risk factor. The decision to use these products in children should be made on a case-by-case basis in consultation with a paediatric infectious disease specialist.*
- *The risk factors that predict progression to severe disease in adults can be used to determine the risk of progression in children aged ≥16 years. In general, paediatric patients should not continue receiving remdesivir, dexamethasone, or other COVID-19-directed therapies following discharge from an ED or an inpatient setting.*

Therapeutic Management of Non-hospitalized Adults With COVID-19

- *Several therapeutic options are now available to treat non-hospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression (Age is the most significant risk factor which starts from at the age of 50 and unvaccinated / not fully vaccinated persons are also at high risk). Several factors affect the selection of the best treatment option for a specific patient.*
- *These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications (i.e., remdesivir), the potential for significant drug-drug interactions (e.g., those associated with the use of ritonavir-boosted nirmatrelvir [Paxlovid]), and the regional prevalence of variants of concern (e.g., the regional prevalence of the Omicron BA.2 subvariant may affect which anti-SARS-CoV-2 monoclonal antibodies [mAbs] can be used for treatment). Table 2a outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for using these therapeutic interventions outside the hospital inpatient setting.*

Risk Stratification for Antiviral therapy

- *Although age is the strongest risk factor for severe COVID-19 outcomes, patients with certain underlying medical conditions are also at higher risk. The more underlying conditions a person has, the higher the risk for severe COVID-19 outcomes. Providers should consider the patient's age, vaccination status, and*

presence of other underlying medical conditions and risk factors in determining the risk of severe COVID-19-associated outcomes for any patient. Among the underlying medical conditions, the listed below are at higher risk based on meta-analysis or systematic review:

- *Asthma*
- *Cancer*
- *Cerebrovascular disease*
- *Chronic kidney disease*
- *Chronic lung disease(COPD, PE, interstitial lung disease, bronchiectasis)*
- *Chronic liver disease*
- *Diabetes Type 1&2*
- *HIV*
- *Heart conditions(heart failure,CAD,CMP)*
- *Mental health conditions(mood disorders, Schizophrenia)*
- *Neurological conditions(dementia)*
- *Obesity*
- *Physical inactivity*
- *Pregnancy and recent pregnancy*
- *Primary immunodeficiency*
- *Smoking(current and former)*
- *Organ/blood stem cell transplant*
- *Use of steroid and other immunosuppressives*
- *Down syndrome*
- *Cystic fibrosis*

Table 2a. Therapeutic Management of Nonhospitalized Adults With COVID-19

Patient Disposition	Panel's Recommendations
Does Not Require Hospitalization or Supplemental Oxygen	**For All Patients:** • All patients should be offered symptomatic management **(AIII)**. • The Panel **recommends against** the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication **(AIIb)**. **For Patients Who Are at High Risk of Progressing to Severe COVID-19**[b] *Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapies. For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab**[f] **(CIII)** • **Molnupiravir**[d,g] **(CIIa)**
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone**[a] **(AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but still require oxygen*[h]	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[i]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not exceed** 10 days) with careful monitoring for AEs **(BIII)**. Because remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[j] clinicians may consider using it in this setting. As remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion	

Table 2b. Dosing Regimens for the Drugs Listed in Table 2a

Drug Name	Dosing Regimen	Time From Symptom Onset[a]
Ritonavir-Boosted Nirmatrelvir (Paxlovid)	**eGFR ≥60 mL/min:** • Nirmatrelvir 300 mg with RTV 100 mg PO twice daily for 5 days **eGFR ≥30 to <60 mL/min:** • Nirmatrelvir 150 mg with RTV 100 mg PO twice daily for 5 days **eGFR <30 mL/min:** • **Not recommended** **Severe Hepatic Impairment (Child-Pugh Class C):** • **Not recommended**	≤5 days
Remdesivir	RDV 200 mg IV on Day 1, followed by RDV 100 mg IV once daily on Days 2 and 3.[b,c] Each infusion should be administered over 30–120 minutes. Patients should be observed for ≥1 hour after infusion as clinically appropriate.	≤7 days

Table 2b. Dosing Regimens for the Drugs Listed in Table 2a, continued

Drug Name	Dosing Regimen	Time From Symptom Onset[a]
Bebtelovimab	BEB 175 mg as a single IV injection, administered over ≥30 seconds. Patients should be observed for ≥1 hour after injection.	≤7 days
Molnupiravir	Molnupiravir 800 mg PO twice daily for 5 days	≤5 days

[a] Per EUA criteria or clinical trial entry criteria.

[b] See the Remdesivir section for a discussion of RDV use in patients with renal impairment.

[c] If RDV is administered to patients who have a new or increasing need for supplemental oxygen but who are discharged from the ED because hospital resources are limited and inpatient admission is not possible, the total duration of therapy is ≤5 days.

Key: BEB = bebtelovimab; ED = emergency department; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; IV = intravenous; PO = orally; RDV = remdesivir; RTV = ritonavir

Rationale for the Use of Specific Agents Listed in Table 2a

- *The Panel's recommendations for the therapeutics that are used to treat nonhospitalized patients with mild to moderate COVID-19 who are at risk of clinical progression are based on the results of clinical trials for the antiviral drugs (ritonavir-boosted nirmatrelvir, remdesivir, and molnupiravir) and on laboratory assessments of the activity of the anti-SARS-CoV-2 mAb bebtelovimab.*
- *Several factors affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy of the treatment option against circulating variants, the availability of the treatment option, the feasibility of administering parenteral medications (i.e., remdesivir, bebtelovimab), and the potential for significant drug-drug interactions (i.e., the interactions associated with using ritonavir-boosted nirmatrelvir).*
- *The Panel recommends ritonavir-boosted nirmatrelvir and remdesivir as preferred therapy options because Phase 3 randomized placebo-controlled trials have reported high clinical efficacies for these agents in patients with COVID-19.3,4 The Panel favors the use of ritonavir-boosted nirmatrelvir in most high-risk, nonhospitalized patients with mild to moderate COVID-19. If ritonavir-boosted nirmatrelvir is not available or cannot be used because of drug-drug interactions, the Panel recommends using remdesivir as the second option.*
- *The Panel recommends bebtelovimab and molnupiravir as alternative therapy options. These drugs should ONLY be used when neither of the preferred treatment options are available, feasible to use, or clinically appropriate. The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for bebtelovimab based on in vitro data that showed that bebtelovimab has activity against all circulating Omicron subvariants and clinical efficacy data from a small, Phase 2 clinical trial in individuals with mild to moderate COVID-19 who were at low risk of disease progression.5 However, there are no Phase 3 clinical trial data for bebtelovimab.*

- *Molnupiravir had lower clinical efficacy in Phase 3 clinical trials than the preferred treatment options. The Panel previously recommended the anti-SARS-CoV-2 mAb sotrovimab as a treatment option for certain nonhospitalized patients with COVID-19.*
- *However, sotrovimab, which is active against the Omicron BA.1 and BA.1.1 subvariants, has substantially decreased in vitro activity against the Omicron BA.2 subvariant.6-8 The distribution of sotrovimab has been paused, and the Panel no longer recommends using sotrovimab to treat COVID-19. There are currently no clinical trial data that directly compare the clinical efficacies of the 4 recommended therapies, and there are no data on the use of combinations of antiviral agents and/ or anti-SARS-CoV-2 mAbs for the treatment of COVID-19. The rationale for each of the Panel's recommendations is discussed below.*

Ritonavir-Boosted Nirmatrelvir (Paxlovid)(Paclovid available in Myanmar)

- *Nirmatrelvir is an orally bioavailable protease inhibitor that is active against MPRO, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.9 It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.10 Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent. Ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range. Recommendations •*
- *The Panel recommends using nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid) orally (PO) twice daily for 5 days in those aged ≥12 years and weighing ≥40 kg; treatment should be initiated as soon as possible and within 5 days of symptom onset (AIIa). •*
- *Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination. • Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient's concomitant medications, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions. • A quick reference guide is also provided in Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications.*
- *The FDA EUA fact sheet for ritonavir-boosted nirmatrelvir, the Liverpool COVID-19 Drug Interactions website, and guidance from the Ontario COVID-19 Science Advisory Table should also be utilized to identify and manage drug-drug interactions. In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 88% compared to placebo in nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.3,11*
- *This efficacy is comparable to the efficacies reported in similar patient populations for remdesivir (87% relative reduction)4 and greater than the efficacy reported for molnupiravir in this setting (30% relative reduction).12*

Ritonavir-boosted nirmatrelvir is expected to be active against all Omicron subvariants, although clinical efficacy data are lacking.

- *Because ritonavir-boosted nirmatrelvir has the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications). However, because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral available for the treatment of COVID-19, drug-drug interactions that can be safely managed should not preclude the use of this medication. Case reports and results from the EPIC-HR trial have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir.*
- *Viral and symptomatic rebound can also occur in the absence of treatment with ritonavir-boosted nirmatrelvir. The frequency, mechanism, and clinical implications of these events are unclear. To date, recurrence of symptoms following the use of ritonavir-boosted nirmatrelvir has not been associated with progression to severe COVID-19. Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized based on the current EUA, and there are insufficient data on the efficacy of administering a second course.*
- *The EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV, which suggests that it has an acceptable safety profile during pregnancy. Based on the mechanisms of action for both nirmatrelvir and ritonavir and the available animal data, the Panel recommends ritonavir-boosted nirmatrelvir for pregnant patients because the potential benefits likely outweigh the risks.*

Box 1. Commonly Prescribed Outpatient Medications Not Expected to Have Clinically Relevant Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Medications Without Clinically Relevant Interactions		
These commonly prescribed medications may be coadministered without dose adjustment and without increased monitoring.[a] This list is not inclusive of all noninteracting medications within each drug category.		
Acid reducing agents	**Diabetes medications**	**Pain medications**
• Famotidine	• Empagliflozin	• Acetaminophen
• Omeprazole	• Insulin	• Aspirin
• Pantoprazole	• Metformin	• Codeine
Allergy medications	• Pioglitazone	• Ibuprofen
• Cetirizine	**Immunosuppressants**	• Naproxen
• Diphenhydramine	• Methotrexate	**Respiratory medications**
• Loratadine	• Mycophenolate	• Corticosteroids (inhaled)
Anti-infective agents	• Prednisone	• Formoterol
• Azithromycin	**Lipid-modifying agents**	• Montelukast
• Hydroxychloroquine	• Ezetimibe	**Miscellaneous**
Cardiovascular agents	• Pitavastatin	• Allopurinol
• Aspirin	• Pravastatin	• Contraceptives (oral)[b]
• Atenolol	**Neuropsychiatric agents**	• Donepezil
• Carvedilol	• Amitriptyline	• Enoxaparin
• Furosemide	• Bupropion	• Finasteride
• Hydrochlorothiazide	• Citalopram	• Levothyroxine
• Irbesartan	• Duloxetine	• Ondansetron
• Isosorbide Dinitrate	• Escitalopram	
• Lisinopril	• Fluoxetine	
• Losartan	• Gabapentin	
• Metoprolol	• Lorazepam	
• Prasugrel	• Nortriptyline	
	• Olanzapine	
	• Paroxetine	
	• Sertraline	
	• Venlafaxine	

Box 2. Outpatient Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Not all medications that may interact with ritonavir-boosted nirmatrelvir are included in Box 2. Deviation from the recommended strategies may be appropriate in certain clinical scenarios.

Prescribe Alternative COVID-19 Therapy		
For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.		
Anticonvulsants	**Cardiovascular agents**	**Pain medications**
• Carbamazepine	• Amiodarone	• Meperidine (pethidine)
• Phenobarbital	• Clopidogrel[a,b]	**Pulmonary hypertension medications**
• Phenytoin	• Disopyramide	• Sildenafil
• Primidone	• Dofetilide	• Tadalafil
Anti-infective agents	• Dronedarone	• Vardenafil
• Glecaprevir/pibrentasvir	• Eplerenone	**Miscellaneous**
• Rifampin	• Flecainide	• Bosentan
• Rifapentine	• Ivabradine	• Certain chemotherapeutic agents[c]
Immunosuppressants	• Propafenone	• Ergot derivatives
• Voclosporin	• Quinidine	• Lumacaftor/ivacaftor
	Neuropsychiatric agents	• St. John's wort
	• Clozapine	• Tolvaptan
	• Lumateperone	
	• Lurasidone	
	• Midazolam (oral)	
	• Pimozide	

Temporarily Withhold Concomitant Medication, If Clinically Appropriate		
Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is elderly or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.		
Anticoagulants • Rivaroxaban[d] **Anti-infective agents** • Erythromycin **BPH medications** • Alfuzosin • Silodosin **Cardiovascular agents** • Aliskiren • Ranolazine • Ticagrelor[b] • Vorapaxar **Immunosuppressants[f]** • Everolimus • Sirolimus • Tacrolimus	**Lipid-modifying agents** • Atorvastatin[e] • Lomitapide • Lovastatin[e] • Rosuvastatin[e] • Simvastatin[e] **Migraine medications** • Eletriptan • Rimegepant • Ubrogepant **Neuropsychiatric agents** • Clonazepam[g] • Clorazepate[g] • Diazepam[g] • Estazolam[g] • Flurazepam[g] • Suvorexant • Triazolam[g]	**Erectile dysfunction medications** • Avanafil **Respiratory medications** • Salmeterol **Miscellaneous** • Certain chemotherapeutic agents[c] • Colchicine[h] • Finerenone • Flibanserin • Naloxegol

Adjust Concomitant Medication Dose and Monitor for Adverse Effects		
Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for specific dosing recommendations.[i] If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.		
Anticoagulants • Apixaban • Dabigatran • Edoxaban **Anti-infective agents** • Clarithromycin • Itraconazole • Ketoconazole • Maraviroc • Rifabutin **BPH medications** • Tamsulosin **Cardiovascular agents** • Cilostazol • Digoxin • Mexiletine **Diabetes medications** • Saxagliptin	**Erectile dysfunction medications** • Sildenafil • Tadalafil • Vardenafil **Immunosuppressants[f]** • Cyclosporine **Neuropsychiatric agents** • Alprazolam[g] • Aripiprazole • Brexpiprazole • Buspirone • Cariprazine • Chlordiazepoxide[g] • Clobazam[g] • Iloperidone • Pimavanserin • Quetiapine • Trazodone	**Pain medications** • Fentanyl • Hydrocodone • Oxycodone **Pulmonary hypertension medications** • Riociguat **Miscellaneous** • Certain chemotherapeutic agents[c] • Darifenacin • Elexacaftor/tezacaftor/ivacaftor • Eluxadoline • Ivacaftor • Tezacaftor/ivacaftor

Remdesivir

- *Remdesivir is currently approved by the FDA for use in hospitalized patients with COVID-19 and in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression. Remdesivir has been studied in nonhospitalized patients with mild to moderate COVID-19 who were at high risk of progressing to severe disease.*
- *The PINETREE trial showed that 3 consecutive days of intravenous (IV) remdesivir resulted in an 87% relative reduction in the risk of*

hospitalization or death compared to placebo.4 Remdesivir is expected to be active against the Omicron variant, although in vitro and in vivo data are currently limited.15 See Remdesivir for more information.

- *Recommendations • The Panel recommends using remdesivir 200 mg IV on Day 1, followed by remdesivir 100 mg IV once daily on Days 2 and 3 in those aged ≥12 years and weighing ≥40 kg; treatment should be initiated as soon as possible and within 7 days of symptom onset (BIIa). •*
- *Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion as clinically appropriate. Because remdesivir requires IV infusions for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings. However, it is an option if ritonavir-boosted nirmatrelvir is not available.*
- *The Panel recommends using remdesivir, dexamethasone, or both drugs together in hospitalized patients who require supplemental oxygen (see Therapeutic Management of Hospitalized Adults With COVID-19). When remdesivir is used in this setting, it is administered as a once-daily IV infusion for 5 days. There are rare instances when hospital resources are limited and admission to an inpatient unit is not possible for patients who need to initiate supplemental oxygen in the emergency department (ED) or who have increasing supplemental oxygen requirements. In these cases, patients may be discharged from the ED with close monitoring and are often prescribed dexamethasone for up to 10 days.*
- *Since remdesivir is often recommended for hospitalized patients with COVID-19 who have similar oxygen needs, clinicians can consider using it in this setting. However, it should be noted that the data on using remdesivir in this situation are limited and administering IV infusions for up to 5 consecutive days can be difficult in the outpatient setting.*

Molnupiravir

- *Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.22,23 Molnupiravir has potent antiviral activity against SARS-CoV-2.23 As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations.*
- *Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results; in the other study, there was no evidence for mutagenicity. The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has*

a low risk for genotoxicity.24 In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA is requiring the manufacturer to establish a process to monitor genomic databases for the emergence of SARS-CoV-2 variants. Molnupiravir is expected to be active against the Omicron variant, although in vitro and in vivo data are currently limited.

- *Recommendation • The Panel recommends using molnupiravir 800 mg PO twice daily for 5 days in those aged ≥18 years ONLY when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate (CIIa). In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo in nonhospitalized patients with COVID-19.*
- *Even though the different treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir and remdesivir are not available or cannot be used, because molnupiravir has lower efficacy than the other options.*
- *The FDA EUA states that molnupiravir is not recommended for use in pregnant patients due to concerns about the instances of fetal toxicity observed during animal studies. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation).*
- *The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy. People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir.*

Dexamethasone For Nonhospitalized Patients With Mild to Moderate COVID-19

- *The Panel recommends against the use of dexamethasone or other systemic glucocorticoids to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen (AIIb). However, patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care providers (AIII).*
- *Medicare and FDA data show a significant increase in the number of prescriptions for systemic corticosteroids among nonhospitalized patients with COVID-19 despite a lack of safety and efficacy data on the use of systemic corticosteroids in this setting. Systemic glucocorticoids may cause harm in nonhospitalized patients with COVID-19.*
- *Results from 1 randomized controlled trial and 1 observational cohort*

study did not demonstrate a clinical benefit of dexamethasone among hospitalized patients who did not require supplemental oxygen, and dexamethasone may potentially cause harm in these patients.

- *In the RECOVERY trial, the use of dexamethasone had no effect on mortality among hospitalized patients with COVID-19 who did not require supplemental oxygen (rate ratio 1.19; 95% CI, 0.91–1.55). A large observational study of patients at Veterans Affairs hospitals reported no survival benefit for dexamethasone among patients with COVID-19 who did not require supplemental oxygen. Instead, these patients had an increased risk of 90-day mortality (HR 1.76; 95% CI, 1.47–2.12).*
- *However, hospitalized patients with COVID-19 are likely to have an increased risk of mortality compared to nonhospitalized patients, which is a limitation of observational trial data. See Table 6a for more information on the clinical trials that evaluated the use of corticosteroids, including dexamethasone.*

For Patients Who Are Discharged From the Hospital and Do Not Require Supplemental Oxygen

- *During the RECOVERY trial, dexamethasone was stopped at the time of hospital discharge. For hospitalized patients with COVID-19 who do not require supplemental oxygen after discharge, the Panel recommends against the continuation of dexamethasone (AIIa).*

For Patients Who Are Discharged From the Hospital and Require Supplemental Oxygen

- *In some cases, adult patients are deemed to be stable enough to be discharged from the inpatient setting even though they still require supplemental oxygen. This practice was likely uncommon during the RECOVERY trial; therefore, there is insufficient evidence for the Panel to recommend either for or against the continued use of dexamethasone after hospital discharge in patients who require supplemental oxygen.*
- *The use of corticosteroids can lead to adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting. If a patient continues to receive corticosteroids after discharge, consider continuing corticosteroids for the duration of supplemental oxygen. However, the total duration of corticosteroid use should not exceed 10 days (including days during hospitalization). Only patients who showed good tolerance to this therapy prior to discharge should continue to receive corticosteroids after discharge.*

For Patients Who Require Hospitalization and Supplemental Oxygen but Were Discharged From the Emergency Department Due to Scarce Resources

- *In rare cases, patients with COVID-19 who require supplemental oxygen and hospital admission may need to be discharged from the ED due to scarce resources (e.g., in cases where hospital beds or staff are not available). For these patients, the Panel recommends using dexamethasone 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events (BIII). These patients should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.*
- *Other Agents That Have Been Studied or Are Under Investigation •*
- *The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin (AI), lopinavir/ritonavir, and other HIV protease inhibitors (AIII) for the outpatient treatment of COVID-19. •*
- *The Panel recommends against the use of antibacterial therapy (e.g., azithromycin, doxycycline) for the outpatient treatment of COVID-19 in the absence of another indication (AIII). • Other agents have undergone or are currently undergoing investigation in the outpatient setting. Antiviral agents, such as ivermectin • Convalescent plasma • Immunomodulators, such as colchicine, fluvoxamine, and inhaled corticosteroids • Supplements, such as vitamin C, vitamin D, and zinc •*
- *The Panel recommends against the use of anticoagulants and antiplatelet therapy for the prevention of venous thromboembolism or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (AIIa). Health care providers should provide information about ongoing clinical trials of investigational therapies to eligible outpatients with COVID-19 so they can make informed decisions about participation (AIII).*

Concomitant Medication Management

- *In general, a patient's usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19 (see Considerations for Using Concomitant Medications in Patients With COVID-19). Angiotensin-converting enzyme inhibitors, statin therapy, nonsteroidal anti-inflammatory drugs, and oral, inhaled, and intranasal corticosteroids that are prescribed for comorbid conditions should be continued as directed (AIII).*
- *Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of SARS-CoV-2.28 In patients with HIV, antiretroviral therapy should not be switched or*

adjusted for the purpose of preventing or treating SARS-CoV-2 infection (AIII). For more information, see Special Considerations in People With HIV.

- *When a patient is receiving an immunomodulating medication, the prescribing clinician should be consulted about the risks and benefits that are associated with a temporary dose reduction or discontinuation. These risks and benefits will depend on the medication's indication and the severity of the underlying condition.*

Symptom Management

- *Symptomatic treatment includes using over-the-counter antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough. Patients with dyspnea may benefit from resting in the prone position rather than the supine position.1*
- *Health care providers should consider educating patients about breathing exercises, as severe breathlessness may cause anxiety.2 Patients should be advised to drink fluids regularly to avoid dehydration.*
- *Rest is recommended as needed during the acute phase of COVID-19, and ambulation and other forms of activity should be increased according to the patient's tolerance. Patients should be educated about the variability in time to symptom resolution and complete recovery.*

Clinical Management of Children Summary

- *Data from the Centers for Disease Control and Prevention demonstrate a lower incidence of SARS-CoV-2 infection, severe disease, and death in children compared with adults.*1-4 *Although only a small percentage of children with COVID-19 will require medical attention, the percentage of intensive care unit admissions among hospitalized children is comparable to the percentage among hospitalized adults with COVID-19.*5-16
- *Risk factors for severe COVID-19 have been identified through observational studies and meta-analyses primarily conducted before the availability of COVID-19 vaccines. Risk factors include having ≥1 severe comorbid conditions, such as medical complexity with respiratory technology dependence, a neurologic condition resulting in impaired mucociliary clearance, obesity (particularly severe obesity), severe underlying cardiac or pulmonary disease, or severely immunocompromised status. However, pediatric data on risk factors for severe COVID-19 are generally more limited and provide lower certainty than data for adults.*
- *In general, COVID-19 has similar clinical manifestations and disease stages in children and adults, including an early phase driven by viral replication and a late phase that appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Respiratory complications in young children that can occur during the early clinical phase include croup and*

bronchiolitis. In addition, a small number of children who have recovered from acute SARS-CoV-2 infection develop multisystem inflammatory syndrome in children (MIS-C) 2 to 6 weeks after infection. MIS-C is a postinfectious inflammatory condition that can lead to severe organ dysfunction, which is in contrast to COVID-19, the acute, primarily respiratory illness due to infection with SARS-CoV-2.

- *There are no results available from clinical trials that evaluated treatments for COVID-19 in children, and data from observational studies are limited. Applying adult data from COVID-19 trials to children is a unique challenge because most children experience a mild course of illness with COVID-19. Relative to adults, children with COVID-19 have substantially lower mortality and less need for hospitalization. Because of these differences in epidemiology and disease severity, the effect sizes for children are likely to be smaller than those observed in adults; therefore, to produce a beneficial outcome, the number needed to treat is higher. Collectively, these factors influence the risk versus benefit balance for pharmacologic therapies in children.*
- *In the absence of sufficient clinical trial data on the treatment of children with COVID-19, the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of children are based largely on adult safety and efficacy data from clinical trials, the child's risk of disease progression, and expert opinion. In general, the older the child and the more severe the disease, the more reasonable it is to follow treatment recommendations for adult patients with COVID 19.*

Table 3a. Therapeutic Management of Nonhospitalized Children With COVID-19

Risk of Severe COVID-19	Panel's Recommendations	
	Aged 12–17 years	Aged <12 years
Symptomatic, Regardless of Risk Factors	• Provide supportive care **(AIII)**.	• Provide supportive care **(AIII)**.

High Risk[a,b]	• Use 1 of the following options (listed in order of preference):[c]
	  • **Ritonavir-boosted nirmatrelvir (Paxlovid)** within 5 days of symptom onset **(BIII)**
	  • **Remdesivir** within 7 days of symptom onset **(CIII)**
	• There is insufficient evidence to recommend either for or against the use of bebtelovimab.[d]
		• Ritonavir-boosted nirmatrelvir is not authorized by the FDA for use in children aged <12 years.
		• There is insufficient evidence to recommend either for or against routine use of remdesivir. Consider treatment based on age and other risk factors.

Intermediate Risk[b,e]	• There is insufficient evidence to recommend either for or against the use of any antiviral therapy. Consider treatment based on age and other risk factors.	• There is insufficient evidence to recommend either for or against routine use of remdesivir.
Low Risk[b,f]	• Manage with supportive care alone **(BIII)**.	• Manage with supportive care alone **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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[a] Molnupiravir is not authorized by the FDA for use in children aged <18 years and should not be used.

[b] See Table 3b for the Panel's framework for assessing the risk of progression to severe COVID-19 based on patient conditions and COVID-19 vaccination status.

[c] Initiate treatment as soon as possible after symptom onset.

[d] Bebtelovimab is the only anti-SARS-CoV-2 mAb active against the current dominant circulating Omicron subvariants. In nonhospitalized adults, bebtelovimab may be used as an alternative therapy when none of the preferred therapies (i.e., ritonavir-boosted nirmatrelvir, remdesivir) are available, feasible to use, or clinically appropriate.

[e] The relative risk of severe COVID-19 for intermediate-risk patients is lower than the risk for high-risk patients but higher than the risk for low-risk patients.

[f] Low-risk patients include those with comorbid conditions that have a weak or unknown association with severe COVID-19. Patients with no comorbidities are included in this group.

Key: FDA = Food and Drug Administration; mAb = monoclonal antibody; the Panel = the COVID-19 Treatment Guidelines Panel

Table 3b. The Panel's Framework for Assessing the Risk of Progression to Severe COVID-19 Based on Patient Conditions and COVID-19 Vaccination Status

Conditions	Risk Level by Vaccination Status[a]		
	Unvaccinated	Primary Series	Up to Date
Strong or Consistent Association With Progression to Severe COVID-19			
• Moderately or severely immunocompromised (see Special Considerations in People Who Are Immunocompromised)	High		
• Obesity (BMI ≥95th percentile for age), especially severe obesity (BMI ≥120% of 95th percentile for age)[b] • Medical complexity with dependence on respiratory technology[c] • Severe neurologic, genetic, metabolic, or other disability that results in impaired airway clearance or limitations in self care or activities of daily living • Severe asthma or other severe chronic lung disease requiring ≥2 inhaled or ≥1 systemic medications daily • Severe congenital or acquired cardiac disease • Multiple moderate to severe chronic diseases	High	Intermediate	
Moderate or Inconsistent Association With Progression to Severe COVID-19			
• Aged <1 year • Prematurity in children aged ≤2 years • Sickle cell disease • Diabetes mellitus (poorly controlled) • Nonsevere cardiac, neurologic, or metabolic disease[d]	Intermediate		
Weak or Unknown Association With Progression to Severe COVID-19			
• Mild asthma • Overweight • Diabetes mellitus (well controlled)	Low		

[a] **Unvaccinated** = individuals who are not eligible for COVID-19 vaccination or are <2 weeks from the final dose of the primary series. **Vaccinated with primary series** = individuals who completed the primary series of 2 or 3 doses (the current CDC term is "fully vaccinated") and are >2 weeks after the final dose of the primary series but have not received a booster, if they are eligible for a booster. Children aged <5 years are not currently eligible for booster doses. **Vaccinated and up to date** = individuals who received the recommended booster dose(s) if eligible or have completed the primary series but are not yet eligible for a booster. See the CDC for more information.

[b] The degree of risk conferred by obesity in younger children is less clear than it is in older adolescents.

[c] Includes tracheostomy or NIV.

[d] Data for this group are particularly limited.

Key: BMI = body mass index; CDC = Centers for Disease Control and Prevention; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel

Prevention of SARS-CoV-2 Infection

Summary Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices **(AI)**.
• The Panel recommends using **tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld)** administered as 2 consecutive 3-mL intramuscular (IM) injections **(BIIb)** as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:
  • Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; *or*
  • Are not able to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components.
• The Panel recommends repeat dosing of **tixagevimab 300 mg plus cilgavimab 300 mg** administered as IM injections every 6 months **(BIIb)**.
• The Food and Drug Administration Emergency Use Authorization states that individuals who received tixagevimab 150 mg plus cilgavimab 150 mg should be given a second dose as soon as possible.
  • If the initial dose was administered ≤3 months prior, the second dose should be tixagevimab 150 mg plus cilgavimab 150 mg.
  • If the initial dose was administered >3 months prior, the second dose should be tixagevimab 300 mg plus cilgavimab 300 mg.
• **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended.**
• The Panel recommends against the use of **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab** for post-exposure prophylaxis (PEP), as the Omicron variant and its subvariants, which are not susceptible to these agents, are currently the dominant SARS-CoV-2 variants circulating in the United States **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

General Prevention Measures

- *Transmission of SARS-CoV-2 is thought to occur primarily through exposure to respiratory droplets. Exposure can occur when someone inhales droplets or particles that contain the virus (with the greatest risk of transmission occurring within 6 feet of an infectious source) or touches their mucous membranes with hands that have been contaminated with the virus. Exhaled droplets or particles can also deposit the virus onto exposed mucous membranes.1*
- *Less commonly, airborne transmission of small droplets and particles of SARS-CoV-2 to people farther than 6 feet away can occur; in rare cases, people passing through a room that was previously occupied by an infectious person may become infected. SARS-CoV-2 infection via airborne transmission of small particles tends to occur after prolonged exposure (i.e., >15 minutes) to an infectious person who is in an enclosed space with poor ventilation.The risk of SARS-CoV-2 transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least 6 feet from others.*
- *When consistent distancing is not possible, face coverings may reduce the spread of infectious droplets from individuals with SARS-CoV-2 infection to others. Frequent handwashing also effectively reduces the risk of infection.2 Health care providers should follow the Centers for Disease Control and Prevention (CDC)*

recommendations for infection control and the appropriate use of personal protective equipment.

Reference:

4. https://www.covid19treatmentguidelines.nih.gov

HELMINTHS PROBLEMS

- **Helminths** (the word is derived from the Greek meaning "worms") have plagued humans since before the era of our earliest recorded history.
- The eggs of intestinal helminths can be found in the mummified feces of humans dating back thousands of years, and we can recognize many of the characteristic clinical features of helminth infections from the ancient writings of Hippocrates, Egyptian medical papyri, and the Bible .
- There are two major phyla of helminths.

I. The nematodes (also known as roundworms) include:

- the major intestinal worms (also known as soil-transmitted helminths)
- the filarial worms that cause lymphatic filariasis (LF) and
- onchocerciasis.

II. the platyhelminths (also known as flatworms) include the flukes (also known as trematodes), such as

- the schistosomes, and
- the tapeworms (also known as the cestodes), such as the pork tapeworm that causes cysticercosis

The most common helminthiases are those caused by infection with

- intestinal helminths,
- ascariasis,
- trichuriasis, and
- hookworm, followed by
- schistosomiasis and
- lymphatic filariasis ,LF .

Table 1

The major human helminthiases and their global prevalence and distribution

Table 1

The major human helminthiases and their global prevalence and distribution

Disease	Major etiologic agent	Global prevalence	Regions of highest prevalence
Soil-transmitted nematodes			
Ascariasis	*Ascariasis lumbricoides* (roundworm)	807 million	Developing regions of Asia, Africa, and Latin America
Trichuriasis	*Trichuris trichiura* (whipworm)	604 million	Developing regions of Asia, Africa, and Latin America
Hookworm	*Necator americanus*; *Ancylostoma duodenale*	576 million	Developing regions of Asia, Africa, and Latin America (especially areas of rural poverty)
Strongyloidiasis	*Strongyloides stercoralis* (thread worm)	30–100 million	Developing regions of Asia, Africa, and Latin America (especially areas of rural poverty)
Filarial nematodes			
LF	*Wuchereria bancrofti*; *Brugia malayi*	120 million	Developing regions of India, Southeast Asia, and sub-Saharan Africa
Onchocerciasis (river blindness)	*Onchocerca volvulus*	37 million	Sub-Saharan Africa
Loiasis	*Loa loa*	13 million	Sub-Saharan Africa
Dracunculiasis (guinea worm)	*Dracunculus medinensis*	0.01 million	Sub-Saharan Africa
Platyhelminth flukes			
Schistosomiasis	*Schistosoma haematobium*; *Schistosoma mansoni*; *Schistosoma japonicum* (blood flukes)	207 million	Sub-Saharan Africa Sub-Saharan Africa and Eastern Brazil China and Southeast Asia
Food-borne trematodiases	*Clonorchis sinensis* (liver fluke); *Opisthorchis viverinni* (liver fluke); *Paragonimus spp.* (lung flukes); *Fasciolopsis buski* (intestinal fluke); *Fasciola hepatica* (intestinal fluke)	>40 million	Developing regions of East Asia
Platyhelminth tapeworms			
Cysticercosis	*Taenia solium* (pork tapeworm)	0.4 million (Latin America only)	Developing regions of Asia, Latin America, and sub-Saharan Africa

SOILTRANSMITTED HELMINTHS (STHS)

Mode of transmission

- Soil-transmitted helminths refer to the intestinal worms infecting humans that are transmitted through contaminated soil ("helminth" means parasitic worm):
- Ascaris lumbricoides (sometimes called just "Ascaris"), approximately 807-1,121 million with Ascaris
- whipworm (Trichuris trichiura), approximately 604-795 million with whipworm
- hookworm (Ancylostoma duodenale and Necator americanus) approximately 576-740 million with hookworm.
- A large part of the world's population is infected with one or more of these soil-transmitted helminths:
- Soil-transmitted helminth infection is found mainly in areas with warm and moist climates where sanitation and hygiene are poor, including in temperate zones during warmer months.
- These STHs are considered neglected tropical diseases (NTDs) because they inflict tremendous disability and suffering yet can be controlled or eliminated.
- Soil-transmitted helminths live in the intestine and their eggs are passed in the feces of infected persons.
- If an infected person defecates outside (near bushes, in a garden, or field) or if the feces of an infected person are used as fertilizer, eggs are deposited on soil.
- Ascaris and hookworm eggs become infective as they mature in soil.
- People are infected with Ascaris and whipworm when eggs are ingested.
- This can happen when hands or fingers that have contaminated dirt on them are put in the mouth or by consuming vegetables and fruits that have not been carefully cooked, washed or peeled.
- Hookworm eggs are not infective. They hatch in soil, releasing larvae (immature worms) that mature into a form that can penetrate the skin of humans.
- Hookworm infection is transmitted primarily by walking barefoot on contaminated soil. One kind of hookworm (Ancylostoma duodenale) can also be transmitted through the ingestion of larvae.
- People with light soil-transmitted helminth infections usually have no symptoms.
- Heavy infections can cause a range of health problems, including abdominal pain, diarrhea, blood and protein loss, rectal prolapse, and physical and cognitive growth retardation.
- Soil-transmitted helminth infections are treatable with medication prescribed by your health care provider.

ASCARIASIS

- An estimated 807 million–1.2 billion people in the world are infected with **Ascaris lumbricoides** (sometimes called just Ascaris or ascariasis).
- Ascaris, hookworm, and whipworm are parasitic worms known as soil-transmitted helminths (STH).
- Together, they account for a major burden of parasitic disease worldwide.
- Ascaris parasites live in the intestine. Ascaris eggs are passed in the feces (poop) of infected people.
- If an infected person defecates outside (for example, near bushes, in a garden, or in a field), or if the feces of an infected person is used as fertilizer, worm eggs are deposited on soil.
- The worm eggs can then grow into a form of the parasite that can infect others. Ascariasis is caused by ingesting those worm eggs.

- This can happen when hands or fingers that have contaminated dirt on them are put in the mouth, or by eating vegetables or fruits that have not been carefully peeled, washed, or cooked.

Epidemiology & Risk Factors

- Ascariasis caused by *Ascaris lumbricoides* is one of the most common intestinal worm infections.
- It is found where access to personal hygiene and proper sanitation practices are not available, and in places where human feces is used as fertilizer.
- Ascariasis caused by *Ascaris suum* is found where there are pigs.
- People who raise pigs or use raw pig manure as fertilizer may be at risk.
- Contact with pigs should be considered when someone is diagnosed with ascariasis.

Geographic Distribution

- *Ascaris lumbricoides* infections happen all over the world.
- The eggs from the parasite are passed in human feces and can contaminate the soil. The eggs survive best in warm, humid areas and must grow in the soil before they can infect others.
- Most cases occur in tropical and subtropical areas of Asia, sub-Saharan Africa, and the Americas
- *Ascaris suum* is found wherever pigs are found
- The standard method for diagnosing ascariasis is by identifying Ascaris eggs in a stool sample using a microscope. Because eggs may be difficult to find in light infections, a concentration procedure is recommended.

Figure: Left/Right: Fertilized eggs of A. lumbricoides in unstained wet mounts of stool.

Center: Adult female A. lumbricoides.

Symptoms

- People with ascariasis often show no symptoms.
- If symptoms occur, they can be light.
- Symptoms include abdominal discomfort or pain. Heavy infections can block the intestines and slow growth in children.
- Other symptoms such as cough are due to migration of the worms through the body. Ascariasis is treatable with medication prescribed by your healthcare provider.
- Humans can also be infected by pig roundworm (Ascaris suum). Ascaris lumbricoides (human roundworm) and Ascaris suum (pig roundworm) are hard to tell apart. It is unknown how many people worldwide are infected with Ascaris suum.

Treatment

- Anthelmintic medications (drugs that remove parasitic worms from the body), such as albendazole and mebendazole, are the drugs of choice for treatment of Ascaris infections, regardless of the species of worm.
- A single dose of albendazole (400 mg),
- Pyrantel pamoate (11 mg/kg; maximum 1 g),
- Ivermectin (150-200 µg/kg) or
- Levimisole 120-150 mg (single dose) or
- Mebendazole (100 mg twice daily for 3 days) is effective for intestinal ascariasis.
- Patients should be warned that they might expel numerous whole, large worms. Obstruction due to ascariasis should be treated with nasogastric suction, piperazine and intravenous fluids.
- Infections are generally treated for 1–3 days.
- The drugs are effective and appear to have few side effects.

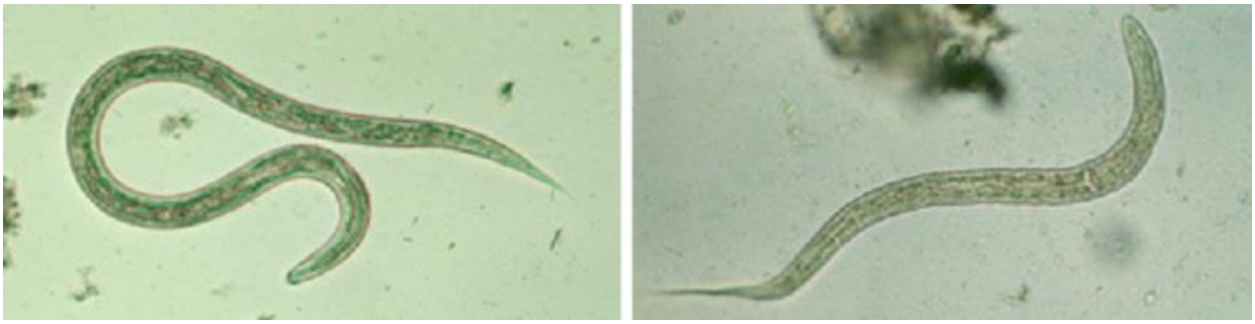
Prevention & Control

- The best way to prevent people from getting ascariasis from humans or pigs is to always do the following:
- Avoid ingesting soil that may be contaminated with human or pig feces, including where human fecal matter ("night soil"), wastewater, or pig manure is used to fertilize crops.
- Wash your hands with soap and water before handling food.
- Wash your hands with soap and water after touching or handling pigs, cleaning pig pens, or handling pig manure.
- Teach children the importance of washing hands to prevent infection.
- Supervise children around pigs, ensuring that they do not put unwashed hands in their mouths.
- Wash, peel, or cook all raw vegetables and fruits before eating, particularly those that have been grown in soil that has been fertilized with manure.
- Transmission of Ascaris lumbricoides infection to others in a community setting can be prevented by: Not defecating outdoors and effective sewage disposal systems.
- More emphasis on: handwashing
- Ascaris suum eggs left in the soil from pigs can survive for up to 10 years. The eggs are very hardy and can survive extreme environmental conditions like freezing and extreme heat.
- It is virtually impossible to completely remove Ascaris suum eggs from the environment where an infected pig has been present.
- Consult a veterinarian for recommendations on preventing and controlling Ascaris suum in your pigs.

HOOKWORM

(Ancylostoma duodenale and Necator americanus)

- An estimated 576-740 million people in the world are infected with hookworm.
- Hookworm, Ascaris, and whipworm are known as soil-transmitted helminths (parasitic worms). Together, they account for a major burden of disease worldwide.
- Hookworms live in the small intestine. Hookworm eggs are passed in the feces of an infected person. If the infected person defecates outside (near bushes, in a garden, or field) or if the feces of an infected person are used as fertilizer, eggs are deposited on soil.
- They can then mature and hatch, releasing larvae (immature worms).
- The larvae mature into a form that can penetrate the skin of humans.
- Hookworm infection is mainly acquired by walking barefoot on contaminated soil.
- One kind of hookworm can also be transmitted through the ingestion of larvae.



- Figure : Left: Filariform (L3) hookworm larva in a wet mount. Right: Hookworm rhabditiform larva (wet preparation)

Symptoms

- Most people infected with hookworms have no symptoms.
- Some have gastrointestinal symptoms, especially persons who are infected for the first time.
- The most serious effects of hookworm infection are blood loss leading to anemia, in addition to protein loss.
- Hookworm infections are treatable with medication prescribed by your health care provider.

Disease

- Highly magnified histologic section showing hookworm (Ancylostoma sp) attached to the intestine.
- High-intensity hookworm infections occur among both school-age children and adults, unlike the soil-transmitted helminths Ascaris and whipworm. High-intensity infections with these worms are less common among adults.
- The most serious effects of hookworm infection are the development of anemia and protein deficiency caused by blood loss at the site of the intestinal attachment of the adult worms.
- When children are continuously infected by many worms, the loss of iron and protein can retard growth and mental development.

Investigation

- The standard method for diagnosing the presence of hookworm is by identifying hookworm eggs in a stool sample using a microscope.
- Because eggs may be difficult to find in light infections, a concentration procedure is recommended.

Treatment

- Anthelminthic medications (drugs that rid the body of parasitic worms),
- such as albendazole and mebendazole, are the drugs of choice for treatment of hookworm infections.
- A single dose of albendazole (400 mg) is the treatment of choice.
- Alternatively, mebendazole 100 mg twice daily for 3 days may be used.
- Infections are generally treated for 1-3 days.
- The recommended medications are effective and appear to have few side effects.
- Iron supplements may also be prescribed if the infected person has anemia.

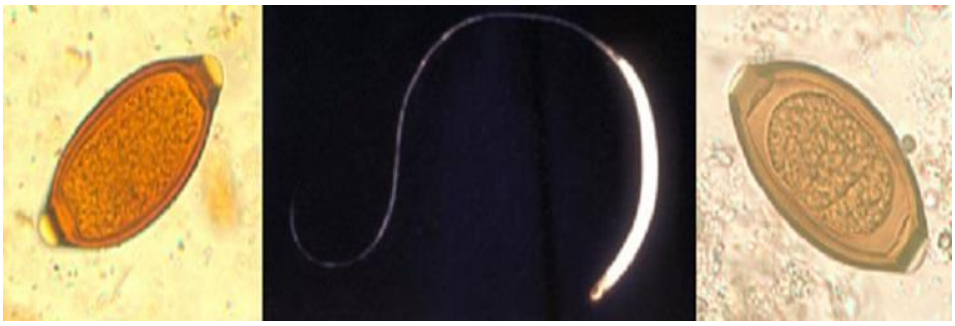
Prevention & Control

- The best way to avoid hookworm infection is not to walk barefoot in areas where hookworm is common and where there may be human fecal contamination of the soil.
- Also, avoid other skin contact with such soil and avoid ingesting it.

- Infection can also be prevented by not defecating outdoors and by effective sewage disposal systems.

TRICHIURIASIS (ALSO KNOWN AS WHIPWORM INFECTION)

- An estimated 604-795 million people in the world are infected with whipworm.
- Whipworm, hookworm, and Ascaris are known as soil-transmitted helminths (parasitic worms).
- They account for a major burden of disease worldwide.
- Whipworms live in the large intestine and whipworm eggs are passed in the feces of infected persons.
- If the infected person defecates outside (near bushes, in a garden, or field) or if human feces as used as fertilizer, eggs are deposited on soil. They can then mature into a form that is infective. Whipworm infection is caused by ingesting eggs.
- This can happen when hands or fingers that have contaminated dirt on them are put in the mouth or by consuming vegetables or fruits that have not been carefully cooked, washed or peeled.
- People infected with whipworm can suffer light or heavy infections. People with light infections usually have no symptoms.
- People with heavy infections can experience frequent, painful bowel movements that contain a mixture of mucus, water, and blood.
- Rectal prolapse (when the rectum sags and comes out of the anus) can also occur. Children with heavy infections can become severely anemic and may grow more slowly. Whipworm infections are treatable with medication prescribed by a health care provider.



- Figure : Left: Egg of T. trichiura in an iodine-stained wet mount. Center: Micrograph of an adult female Trichuris human whipworm that is approximately 4cm long. Right: Egg of T. trichiura in an unstained wet mount.

Disease

- People infected with whipworm can suffer light or heavy infections. People with light infections usually have no symptoms.
- People with heavy symptoms can experience frequent, painful passage of stool that contains a mixture of mucus, water, and blood.
- Rectal prolapse can also occur.
- Heavy infection in children can lead to severe anemia, growth retardation, and impaired cognitive development. Whipworm infections are treatable with medication prescribed by your health care provider.
- The standard method for diagnosing the presence of whipworm is by microscopically identifying whipworm eggs in a stool sample. Because eggs may be difficult to find in light infections, a concentration procedure is recommended.

Treatment

- Anthelminthic medications (drugs that rid the body of parasitic worms), such as albendazole and mebendazole, are the drugs of choice for treatment.
- Infections are generally treated for 3 days. The recommended medications are effective. Health care providers may decide to repeat a stool exam after treatment.
- Iron supplements may also be prescribed if the infected person suffers from anemia.

Prevention & Control

- The best way to prevent whipworm infection is to always:
- Avoid ingesting soil that may be contaminated with human feces, including where human fecal matter ("night soil") or wastewater is used to fertilize crops.
- Wash your hands with soap and warm water before handling food.
- Teach children the importance of washing hands to prevent infection.
- Wash, peel, or cook all raw vegetables and fruits before eating, particularly those that have been grown in soil that has been fertilized with manure.
- More focus on: Handwashing
- Transmission of infection to others can be prevented by: Not defecating outdoors and effective sewage disposal systems.

STRONGYLOIDIASIS

- *Strongyloides stercoralis* is a very small nematode (2 mmx 0.4 mm) which parasitises the mucosa of the upper part of the small intestine, often in large numbers, causing persistent eosinophilia.
- The eggs hatch in the bowel but only larvae are passed in the faeces.
- In moist soil, they mould and become the infective filariform larvae.
- After penetrating human skin, they undergo a development cycle similar to that of hookworms, except that the female worms burrow into the intestinal mucosa and submucosa.
- Some larvae in the intestine may develop into filariform larvae, which may then penetrate the mucosa or the perianal skin and lead to autoinfection and persistent infection.
- Patients with Strongyloides infection persisting for more than 35 years have been described.
- Strongyloidiasis occurs in the tropics and subtropics.

Clinical features of strongyloidiasis

- Penetration of skin by infective larvae
    - Itchy rash
- Presence of worms in gut
    - Abdominal pain, diarrhoea, steatorrhoea, weight loss
- Allergic phenomena
    - Urticarial plaques and papules, wheezing, arthralgia
- Autoinfection
    - Transient itchy, linear, urticarial weals across abdomen and buttocks (larva currens)
- Systemic (super) infection
    - Diarrhoea, pneumonia, meningoencephalitis, death
- The classic triad of symptoms consists of abdominal pain, diarrhoea and urticaria.
- Cutaneous manifestations, either urticaria or larva currens (a highly characteristic pruritic, elevated, erythematous lesion advancing along the course of larval migration), are

characteristic and occur in 66% of patients.

- Systemic strongyloidiasis (the Strongyloides hyperinfection syndrome), with dissemination of larvae throughout the body, occurs in association with immune suppression (intercurrent disease, HIV and HTLV-1 infection, corticosteroid treatment).
- Patients present with severe, generalised abdominal pain, abdominal distension and shock. Massive larval invasion of the lungs causes cough, wheeze and dyspnoea; cerebral involvement has manifestations ranging from subtle neurological signs to coma.
- Gram-negative sepsis frequently complicates the picture.

Investigations

- There is eosinophilia. Serology (ELISA) is helpful but definitive diagnosis depends upon finding the larvae.
- The faeces should be examined microscopically for motile larvae; excretion is intermittent and so repeated examinations may be necessary.
- Larvae can also be found in jejunal aspirate or detected using the string test (p. 369). Larvae may also be cultured from faeces.

Management

- A course of two doses of ivermectin (200 µg/kg), administered on successive days, is effective.
- Alternatively, albendazole is given orally in a dose of 15 mg/kg body weight twice daily for 3 days. A second course may be required.
- For the Strongyloides hyperinfection syndrome, ivermectin is given 200 µg/kg for 5-7 days.

FILARIASIS OR LYMPHATIC FILARIASIS

- It is Filarial nematodes
- Lymphatic filariasis impairs the lymphatic system and can lead to the abnormal
- An essential, recommended package of care can alleviate suffering and prevent further disability among people living with disease caused by lymphatic filariasis.
- Lymphatic filariasis, commonly known as elephantiasis, is a neglected tropical disease. Infection occurs when filarial parasites are transmitted to humans through mosquitoes. Infection is usually acquired in childhood causing hidden damage to the lymphatic system.
- The painful and profoundly disfiguring visible manifestations of the disease, lymphoedema, elephantiasis and scrotal swelling occur later in life and can lead to permanent disability. These patients are not only physically disabled, but suffer mental, social and financial losses contributing to stigma and poverty.
- In 2020, 863 million people in 50 countries were living in areas that require preventive chemotherapy to stop the spread of infection.
- The global baseline estimate of people affected by lymphatic filariasis was 25 million men with hydrocele and over 15 million people with lymphoedema. At least 36 million people remain with these chronic disease manifestations. Eliminating lymphatic filariasis can prevent unnecessary suffering and contribute to the reduction of poverty.

Cause and transmission

- Lymphatic filariasis is caused by infection with parasites classified as nematodes (roundworms) of the family Filariodidea.
- There are 3 types of these thread-like filarial worms:
- *Wuchereria bancrofti*, which is responsible for 90% of the cases
- *Brugia malayi*, which causes most of the remainder of the cases

- *Brugia timori*, which also causes the disease.
- Adult worms nest in the lymphatic vessels and disrupt the normal function of the lymphatic system. The worms can live for approximately 6–8 years and, during their lifetime, produce millions of microfilariae (immature larvae) that circulate in the blood.
- Mosquitoes are infected with microfilariae by ingesting blood when biting an infected host. Microfilariae mature into infective larvae within the mosquito.
- When infected mosquitoes bite people, mature parasite larvae are deposited on the skin from where they can enter the body.
- The larvae then migrate to the lymphatic vessels where they develop into adult worms, thus continuing a cycle of transmission.
- Lymphatic filariasis is transmitted by different types of mosquitoes for example by the Culex mosquito, widespread across urban and semi-urban areas, Anopheles, mainly found in rural areas, and *Aedes*, mainly in endemic islands in the Pacific.

Symptoms

- Lymphatic filariasis infection involves asymptomatic, acute, and chronic conditions. The majority of infections are asymptomatic, showing no external signs of infection while contributing to transmission of the parasite.
- These asymptomatic infections still cause damage to the lymphatic system and the kidneys and alter the body's immune system.
- When lymphatic filariasis develops into chronic conditions it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and hydrocele (scrotal swelling).
- Involvement of breasts and genital organs is common. Such body deformities often lead to social stigma and sub-optimal mental health, loss of income-earning opportunities and increased medical expenses for patients and their caretakers.
- Acute episodes of local inflammation involving skin, lymph nodes and lymphatic vessels often accompany chronic lymphoedema or elephantiasis. Some of these episodes are caused by the body's immune response to the parasite.
- Most are the result of secondary bacterial skin infection where normal defenses have been partially lost due to underlying lymphatic damage.
- These acute attacks are debilitating, may last for weeks and are the primary cause of lost wages among people suffering with lymphatic filariasis.

Large-scale treatment (preventive chemotherapy)

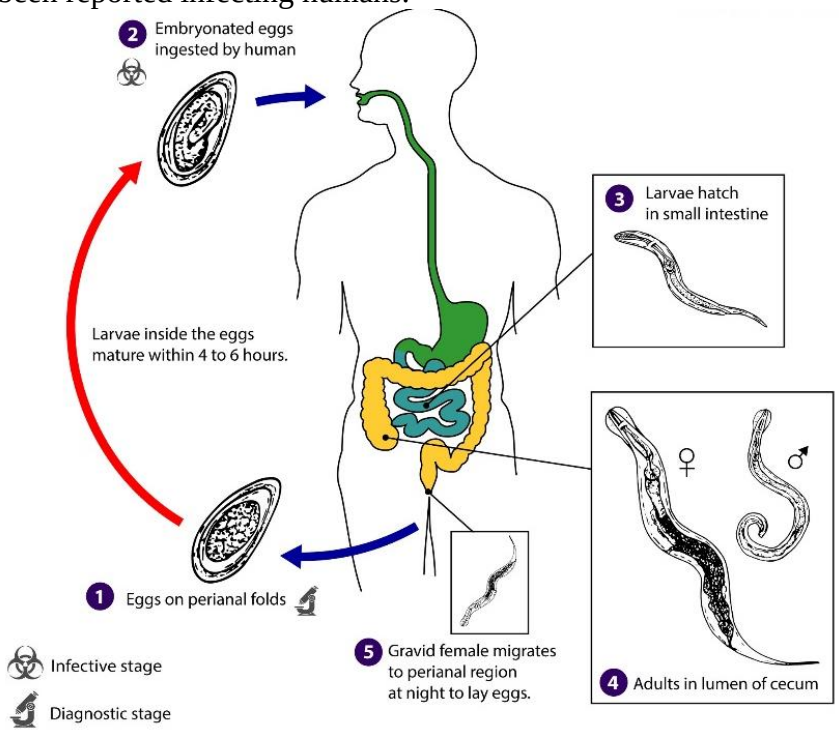
- Elimination of lymphatic filariasis is possible by stopping the spread of the infection through preventive chemotherapy.
- The WHO recommended preventive chemotherapy strategy for lymphatic filariasis elimination is mass drug administration (MDA).
- MDA involves administering an annual dose of medicines to the entire at-risk population. The medicines used have a limited effect on adult parasites but effectively reduce the density of microfilariae in the bloodstream and prevent the spread of parasites to mosquitoes.
- The mass drug administration (MDA) regimen recommended depends on the co-endemicity of lymphatic filariasis with other filarial diseases.
- WHO recommends the following MDA regimens:
    - albendazole (400 mg) alone twice per year for areas co-endemic with loiasis
    - ivermectin (200 mcg/kg) with albendazole (400 mg) in countries with onchocerciasis
    - diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in countries without onchocerciasis
- Recent evidence indicates that the combination of all three medicines can safely clear almost all microfilariae from the blood of infected people within a few weeks, as opposed to years using the routine two-medicine combination.

- WHO now recommends the following MDA regimen in countries without onchocerciasis:
    - ivermectin (200 mcg/kg) together with diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in certain settings
- The impact of MDA depends on the efficacy of the regimen and the coverage (proportion of total population ingesting the medicines). MDA with the two-medicine regimens have interrupted the transmission cycle when conducted annually for at least 4–6 years with effective coverage of the total population at risk. Salt fortified with DEC has also been used in a few unique settings to interrupt the transmission cycle.
- Success in 2030 will be achieved if people affected by lymphatic filariasis have access to the following essential package of care:
    - treatment for episodes of adenolymphangitis (ADL);
    - guidance in applying simple measures to manage lymphoedema to prevent progression of disease and debilitating, inflammatory episodes of ADL;
    - surgery for hydrocele;
    - treatment for infection
    - **Vector control**
    - Mosquito control is a supplemental strategy supported by WHO. It is used to reduce transmission of lymphatic filariasis and other mosquito-borne infections.

ENTEROBIUS VERMICULARIS (THREADWORM)

Causal Agent

- The nematode (roundworm) *Enterobius vermicularis* is widely known as the human pinworm due to the female's long, pointed tail.
- In some areas the common names "seatworm" and "threadworm" are used (the latter of which is sometimes also used to refer to *Strongyloides stercoralis*).
- Another putative pinworm species, *Enterobius gregorii*, has been described and reported from humans in Europe, Africa, and Asia.
- However, further morphologic and molecular evidence suggests *E. gregorii* likely represents an immature form of *E. vermicularis.* The rat pinworm, *Syphacia obvelata*, has also very rarely been reported infecting humans.



Life cycle of enterobius vermicularis

Source: https://www.cdc.gov/dpdx/enterobiasis/modules/Enterobius_LifeCycl_lg.jpg

- Gravid adult female *Enterobius vermicularis* deposit eggs on perianal folds.
- Infection occurs via self-inoculation (transferring eggs to the mouth with hands that have scratched the perianal area) or through exposure to eggs in the environment (e.g. contaminated surfaces, clothes, bed linens, etc.).
- Following ingestion of infective eggs, the larvae hatch in the small intestine
- and the adults establish themselves in the colon, usually in the cecum.
- The time interval from ingestion of infective eggs to oviposition by the adult females is about one month. At full maturity adult females measure 8 to 13 mm, and adult males 2 to 5 mm; the adult life span is about two months. Gravid females migrate nocturnally outside the anus and oviposit while crawling on the skin of the perianal area.
- The larvae contained inside the eggs develop (the eggs become infective) in 4 to 6 hours under optimal conditions.
- Rarely, eggs may become airborne and be inhaled and swallowed. Retroinfection, or the migration of newly hatched larvae from the anal skin back into the rectum, may occur but the frequency with which this happens is unknown.

Hosts

- Oxyurid nematodes (pinworms) generally exhibit high host specificity. Humans are considered the only host for *E. vermicularis,* although occasional infections have been reported in captive chimpanzees.

Geographic Distribution

- *E. vermicularis* occurs worldwide, with infections occurring most frequently in school- or preschool-children and in crowded conditions.

Clinical Presentation

- Enterobiasis is frequently asymptomatic. The most typical symptom is perianal pruritus, especially at night, which may lead to excoriations and bacterial superinfection. Occasionally, invasion of the female genital tract with vulvovaginitis and pelvic or peritoneal granulomas can occur.
- Other symptoms include, teeth grinding, enuresia, insomnia, anorexia, irritability, and abdominal pain, which can mimic appendicitis.
- *E. vermicularis* larvae are often found within the appendix on appendectomy, but the role of this nematode in appendicitis remains controversial.
- Very rare instances of eosinophilic colitis associated with *E. vermicularis* larvae have been reported.

Treatment

- Mebendazole is the drugs of choice, taken by mouth. Dosage in children from 6 months to 17 years is 100 mg for one dose, if reinfection occur, second dose may be needed after two weeks. In adult, dosage is 100mg for one dose, if reinfection occur, second dose may be needed after two weeks.
- Albendazole (400 mg), pyrantel pamoate (11 mg/kg) or piperazine (4 g) is given and may be repeated after 2 weeks to control auto-reinfection.
- If infection recurs in a family, each member should be treated as above. During this all nightclothes and bed linen are laundered. Fingernails must be kept short and hands washed carefully before meals.
- A bath taken immediately after rising will remove ova laid during the night. Subsequent therapy is reserved for those family members who develop recurrent infection.

LOIASIS

- Loiasis is caused by infection with the filaria Loa loa. The adult worms, 3- 7 cm x 4 mm, chiefly parasitise the subcutaneous tissue of humans, releasing larval microfilariae into the peripheral blood in the daytime.
- The vector is Chrysops, a forest-dwelling, day-biting fly.
- The host response to Loa loa is usually absent or mild, so that the infection may be harmless.
- From time to time a short-lived, inflammatory, oedematous swelling (a Calabar swelling) is produced around an adult worm. Heavy infections, especially when treated, may cause encephalitis.

Clinical features

- The infection is often symptomless. The incubation period is commonly over a year but may be just 3 months. The first sign is usually a Calabar swelling, an irritating, tense, localised swelling that may be painful, especially if it is near a joint.
- The swelling is generally on a limb; it measures a few centimetres in diameter but sometimes is more diffuse and extensive. It usually disappears after a few days but may persist for 2 or 3 weeks.
- A succession of such swellings may appear at irregular intervals, often in adjacent sites. Sometimes, there is urticaria and pruritus elsewhere.
- Occasionally, a worm may be seen wriggling under the skin, especially that of an eyelid, and may cross the eye under the conjunctiva, taking many minutes to do so.

Investigations

- Diagnosis is by demonstrating microfilariae in blood taken during the day, but they may not always be found in patients with Calabar swellings.
- Antifilarial antibodies are positive in 95% of patients and there is massive eosinophilia. Occasionally, a calcified worm may be seen on X-ray.

Management

- Diethylcarbamazine (DEC) is curative, in a dose of 9-12 mg/kg daily, continued for 21 days.
- Treatment may precipitate a severe reaction in patients with a heavy microfilaraemia characterised by fever, joint and muscle pain, and encephalitis; microfilaraemic patients should be given corticosteroid cover.

Prevention

- Protection is afforded by building houses away from trees and by having dwellings wire screened. Protective clothing and insect repellents are also useful.
- Diethylcarbamazine (DEC) in a dose of 5 mg/kg daily for 3 days each month is partially protective.

CESTODES (TAPEWORMS)

- Cestodes are ribbon-shaped worms which inhabit the intestinal tract. They have no alimentary system and absorb nutrients through the tegumental surface. The anterior end, or scolex, has suckers for attaching to the host.
- From the scolex, a series of progressively developing segments arise, the proglottides, which may continue to show active movements when shed. Cross-fertilisation takes place between segments. Ova, present in large numbers in mature proglottides, remain viable for weeks, and during this period, they may be consumed by the intermediate host.
- Larvae liberated from the ingested ova pass into the tissues, forming larval cysticerci.

Tapeworms cause two distinct patterns of disease, either intestinal infection or systemic cysticercosis.

- Taenia saginata (beef tapeworm), Taenia asiatica and Diphyllobothrium latum (fish tapeworm) cause only intestinal infection, following human ingestion of intermediate hosts that contain cysticerci (the larval stage of the tapeworm). Taenia solium causes intestinal infection.
- If a cysticerci-containing intermediate host is ingested, and cysticercosis (systemic infection from larval migration) if ova are ingested. Echinococcus granulosus (dog tapeworm) does not cause human intestinal infection, but causes hydatid disease (which is analogous to cysticercosis) following ingestion of ova and subsequent larval migration.

INTESTINAL TAPEWORM

- Humans acquire tapeworm by eating undercooked beef infected with the larval stage of T. saginata, undercooked pork containing the larval stage of T. solium or T. asiatica, or undercooked freshwater fish containing larvae of D. latum.
- Usually, only one adult tapeworm is present in the gut but up to ten have been reported. The ova of all the three Taenia are indistinguishable microscopically.
- However, examination of scolex and proglottides candifferentiate: T. solium has a rostellum and two rows of hooklets on the scolex, and discharges multiple proglottides (3-5) attached together with lower degrees of uterine branching (approximately 10);
- T. saginata has only four suckers in its scolex, and discharges single proglottids with greater uterine branching (up to 30); T. asiatica has a rostellum without hooks on its scolex, and is difficult to differentiate from T. saginata, except that there are fewer uterine branches (16-21).

TAENIA SAGINATA

- Infection with *T. saginata* occurs in all parts of the world.
- The adult worm may be several metres long and produces little or no intestinal upset in human beings, but knowledge of its presence, by noting segments in the faeces or on underclothing, may distress the patient.
- Ova may be found in the stool.
- Praziquantel is the drug of choice; niclosamide or nitazoxanide is an alternative. Prevention depends on efficient meat inspection and the thorough cooking of beef.

TAENIA SOLIUM

- *T. solium,* the pork tapeworm, is common in central Europe, South Africa, South America and parts of Asia.
- It is not as large as *T. saginata.* The adult worm is found only in humans following the eating of undercooked pork containing cysticerci.
- Intestinal infection is treated with praziquantel (5- 10 mg/kg) or niclosamide (2 g), both as a single dose, or alternatively with nitazoxanide (500 mg twice daily for 3 days).
- These are followed by a mild laxative (after 1-2 hours) to prevent retrograde intestinal autoinfection.
- Cooking pork well prevents intestinal infection. Great care must be taken while attending a patient harbouring an adult worm to avoid ingestion of ova or segments.

TAENIA ASIATICA

- *T. asiatica* is a newly recognised species of *Taenia,* restricted to Asia. It is acquired by eating

uncooked meat or viscera of pigs.
- Clinical features and treatment are similar to those of *T. saginata.*

CYSTICERCOSIS

- Human cysticercosis is acquired by ingesting *T. solium* tapeworm ova, from either contaminated fingers or food.
- The larvae are liberated from eggs in the stomach, penetrate the intestinal mucosa and are carried to many parts of the body, where they develop and form cysticerci, 0.5-1 cm cysts that contain the head of a young worm.
- They do not grow further or migrate. Common locations are the subcutaneous tissue, skeletal muscles and brain.

Clinical features

- When superficially placed, cysts can be palpated under the skin or mucosa as pea-like ovoid bodies.
- Here they cause few or no symptoms, and will eventually die and become calcified. Heavy brain infections, especially in children, may cause features of encephalitis.
- More commonly, however, cerebral signs do not occur until the larvae die, 5-20 years later.
- Epilepsy, personality changes, staggering gait or signs of hydrocephalus are the most common features.

Investigations

- Calcified cysts in muscles can be recognised radiologically.
- In the brain, however, less calcification takes place and larvae are only occasionally visible by plain X-ray; usually CT or MRI will show them.
- Epileptic fits starting in adult life suggest the possibility of cysticercosis if the patient has lived in or travelled to an endemic area.
- The subcutaneous tissue should be palpated and any nodule excised for histology. Radiological examination of the skeletal muscles may be helpful. Antibody detection is available for serodiagnosis

Management and prevention

- Albendazole, 15 mg/kg daily for a minimum of 8 days, has now become the drug of choice for parenchymal neurocysticercosis.
- Praziquantel is another option, 50 mg/kg in three divided doses daily for 10 days.
- Prednisolone, 10 mg 3 times daily, is also given for 14 days, starting 1 day before the albendazole or praziquantel.
- In addition, anti-epileptic drugs should be given until the reaction in the brain has subsided. Operative intervention is indicated for hydrocephalus. Studies from India and Peru suggest that most small, solitary cerebral cysts will resolve without treatment.

ECHINOCOCCUS GRANULOSUS HYDATID DISEASE (TAENIA ECHINOCOCCUS)

- Dogs are the definitive hosts of the tiny tapeworm *E. granulosus.* The larval stage, a hydatid cyst, normally occurs in sheep, cattle, camels and other animals that are infected from contaminated pastures or water.
- By handling a dog or drinking contaminated water, humans may ingest eggs. The embryo is liberated from the ovum in the small intestine and gains access to the blood stream and

thus to the liver.

- The resultant cyst grows very slowly, sometimes intermittently. It is composed of an enveloping fibrous pericyst, laminated hyaline membrane (ectocyst) and inner germinal layers (endocyst) which gives rise to daughter cysts, or germinating cystic brood capsule in which larvae (protoscolices) develop.
- Over time, some cysts may calcify and become non-viable. The disease is common in the Middle East, North and East Africa, Australia and Argentina.
- *E. multilocularis*, which has a cycle between foxes and voles, causes a similar but more severe infection, 'alveolar hydatid disease', which invades the liver like cancer.

Clinical features

- A hydatid cyst is typically acquired in childhood and may, after growing for some years, cause pressure symptoms. These vary, depending on the organ or tissue involved. In nearly 75% of patients with hydatid disease, the right lobe of the liver is invaded and contains a single cyst. In others, a cyst may be found in lung, bone, brain or elsewhere.

Investigations

- The diagnosis depends on the clinical, radiological and ultrasound findings in a patient who has lived in close contact with dogs in an endemic area.
- Complement fixation and ELISA are positive in 70-90% of patients.

Management and prevention

- Hydatid cysts should be excised wherever possible. Great care is taken to avoid spillage and cavities are sterilised with 0.5% silver nitrate or 2.7% sodium chloride. Albendazole (400 mg twice daily for 3 months) should also be used.
- The drug is now often combined with PAIR (percutaneous puncture, aspiration, injection of scolicidal agent and re-aspiration) to good effect.
- Praziquantel (20 mg/kg twice daily for 14 days) also kills protoscolices perioperatively.

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