



Assessing, Managing and Monitoring Biologic Therapies for Inflammatory Arthritis

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Biologic Drugs

Biological therapy	Abbreviation	Mechanism of action
Adalimumab	ADA	Anti-TNF α
Certolizumab pegol	CZB	Anti-TNF α
Etanercept	ETN	Anti-TNF α
Golimumab	GOL	Anti-TNF α
Infliximab	INF	Anti-TNF α
Rituximab	RTX	Anti-CD20
Tocilizumab	TCZ	Anti-IL-6 receptor
Ustekinumab	UST	Anti-IL-12/IL-23
Abatacept	ABA	CTLA4-Ig

History

- Auto immune conditions such as lupus
- Neurological disorders such as MS
- Previous TB exposure and treatment
- Cardiac disorders such as heart failure (CCF), IHD, arrhythmias
- Hepatic impairment, disease such as viral hepatitis
- Hematological disease (pancytopenia, aplastic anaemia)
- Pulmonary/lung disease – such as ILD, COPD
- Uveitis
- Diabetes (Etanercept)

History

- History of psoriasis, prolonged PUVA(anti-TNF α)
- Any planned surgery
- Current or planned pregnancy/ breastfeeding/contraception plans
- Any allergies including latex(ustekinumab and secukinumab)
- Diverticulitis and hyperlipidaema (tocilizumab)
- Malignancies (including skin) and Check for risks of malignancy :
 - Ulcerative colitis, Barrett's oesophagus, History of smoking, Cervical dysplasia
 - Large bowel polyps or family history of malignancy
- Recent live vaccine (recommended that a period of at least four weeks)

Pre-treatment investigations

- Full blood count(FBC)
- Creatinine/calculated GFR
- (ALT) and (AST), albumin, (Tocilizumab and Infliximab)
- Baseline lipid profile (TCZ)
- Hepatitis B and C serology (HBsAg), (HBcAb), (HCV Ab)
- Tuberculin skin test(TST) and/or IFN-g release assay (IGRA)
- Baseline immunoglobulins (IgA, IgG and IgM) (RTX)
- Chest radiography

Pre-treatment investigations

- ANA, (if positive ENA/ds-DNA)
- Blood pressure check
- Suspected malignancy should be investigated
- Check for hypogammaglobulinaemia before starting(belimumab)
- Check current APPT status if on heparin (certolizumab pegol)
- Flu and Pneumonia vaccination
- Varicella zoster serology (varicella IgG levels)
- MMR screening /previous measles infection (Measles IgG)

Contra-indications, special warnings

- Infection (including skin), sepsis or risk of sepsis, TB, hepatitis, HIV
Consider using ETN or ABA as a first line biologic therapy in patients at high risk of infection
- Hypersensitivity to the active substances or to any of the excipients
- Hypogammaglobulinaemia or very low levels of CD4 or CD8 (RTX)
- Hepatic impairment and baseline ALT or AST is $> 5 \times$ ULN (TCZ,INF)
- Significant hematological abnormalities

Contra-indications, special warnings

- lupus diagnosis
- Clear history of multiple sclerosis (MS)
- Moderate/Severe congestive cardiac failure (class/grade III/IV)
- History of having received a recent live vaccine(<4W)
- Hereditary problems of fructose intolerance(golimumab)
- Septic arthritis of a native joint within the last 12 months

Vaccinations

- Influenza and pneumococcal immunization
- Hepatitis B
- Tetanus
- Papillomavirus vaccine
- Measles, Mumps and Rubella (MMR) *LIVE
- BCG *LIVE
- Oral Polio *LIVE
- Varicella zoster (VZ) *LIVE

Contraindication of Live vaccines

>40 mg/d prednisolone for >1week within the past 3 months

>20 mg/d prednisolone for >14 days within the past 3 months

MTX >25 mg/week, AZA >3.0 mg/kg/day

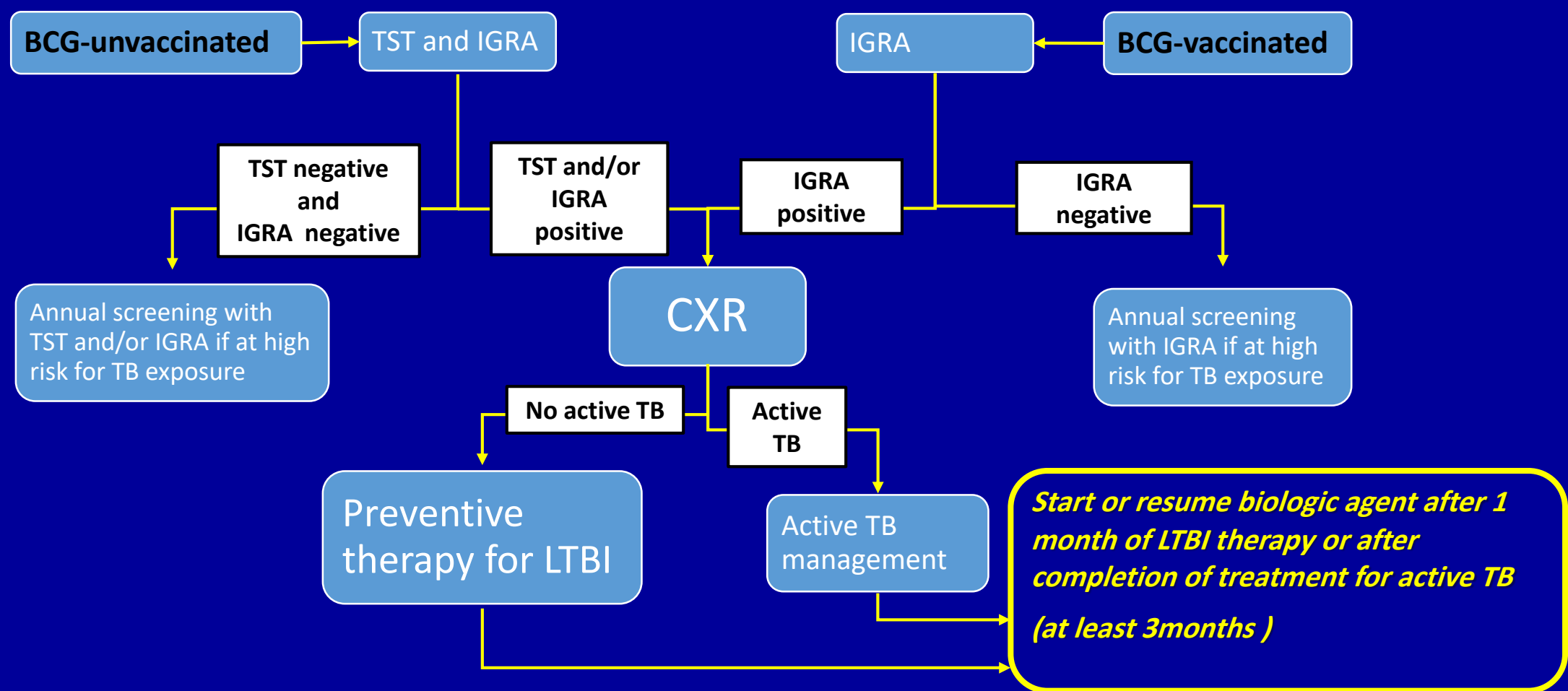
other types of immunosuppressive drugs cyclosporin, leflunomide,

Biologics (past 12 months)

Live vaccines

- Administer ≥ 4 weeks before biologic initiation or wait ≥ 3 half-lives after stopping biologic therapy
- There is no contraindication for the administration of live vaccines to relatives or friends of patients having biologic therapies.
- Individuals who are changing the nappies of young children should be advised to wear gloves.

Recommendations for Screening and Management of Latent and Active TB Infection in Patients Requiring Biologic Therapy



CXR=chest x-ray; IGRA=interferon gamma release assay; BCG=Bacillus Calmette-Guérin; TST= tuberculin skin test.
Cantini F et al. *Autoimmun Rev.* 2015;14:503-509.

Recommends treatment for latent TB

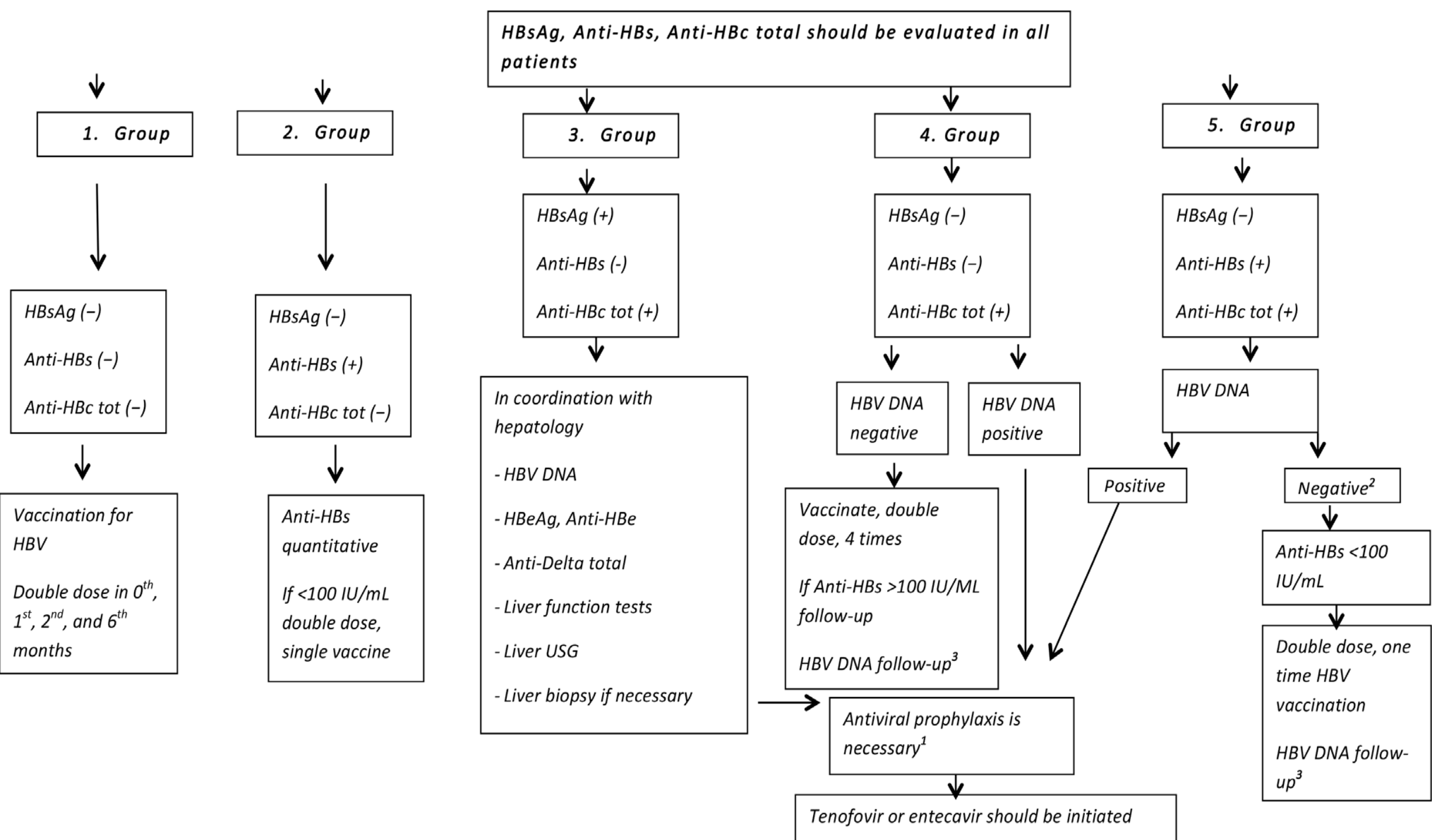
• Positive IGRA or • TST>5 mm	>15 mg/day of prednisolone for 1 month or longer - Taking anti-TNFs - HIV-infected individuals - Organ transplants - Fibrotic changes on CXR consistent with prior TB
• Positive IGRA or • TST>10 mm	- Recent immigrants (<5 years) from high-prevalence countries - Injection drug users and residents and employees in high-risk settings (nursing homes and hospitals)
• Positive IGRA or • TST>15 mm	with no known risk factors for TB

Investigations for latent TB infection

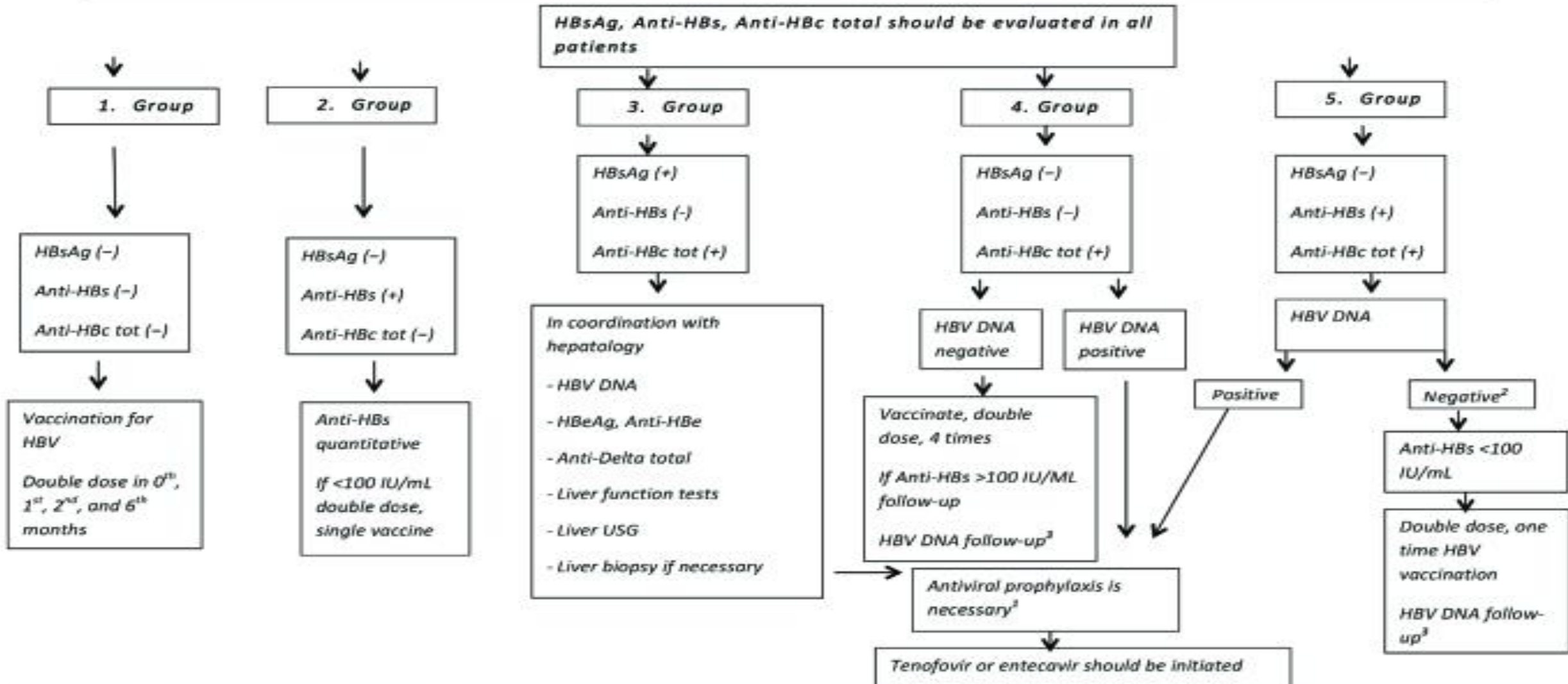
- Screening with TST or IGRA is unhelpful in patients who have had treatment for active or latent TB. In this situation a chest X-ray and sputum examination will be sufficient
- ETN should be considered as a first-line anti-TNF treatment in patients at high risk of reactivation of latent TB.

Patient groups according to viral hepatitis screening

- Group 1 HBV seronegatives
- Group 2 Immunized with vaccine
- Group 3 With previous HBV infection
- Group 4 With chronic HBV infection
- Group 5 With healed HBV infection-Naturally immunized



Recommendations for HBV screening and prophylaxis in the patients to be administered with biological DMARDs such as TNF inhibitor, rituximab, tocilizumab, abatacept, target oriented DMARD, or >7.5 mg/day of prednisolone

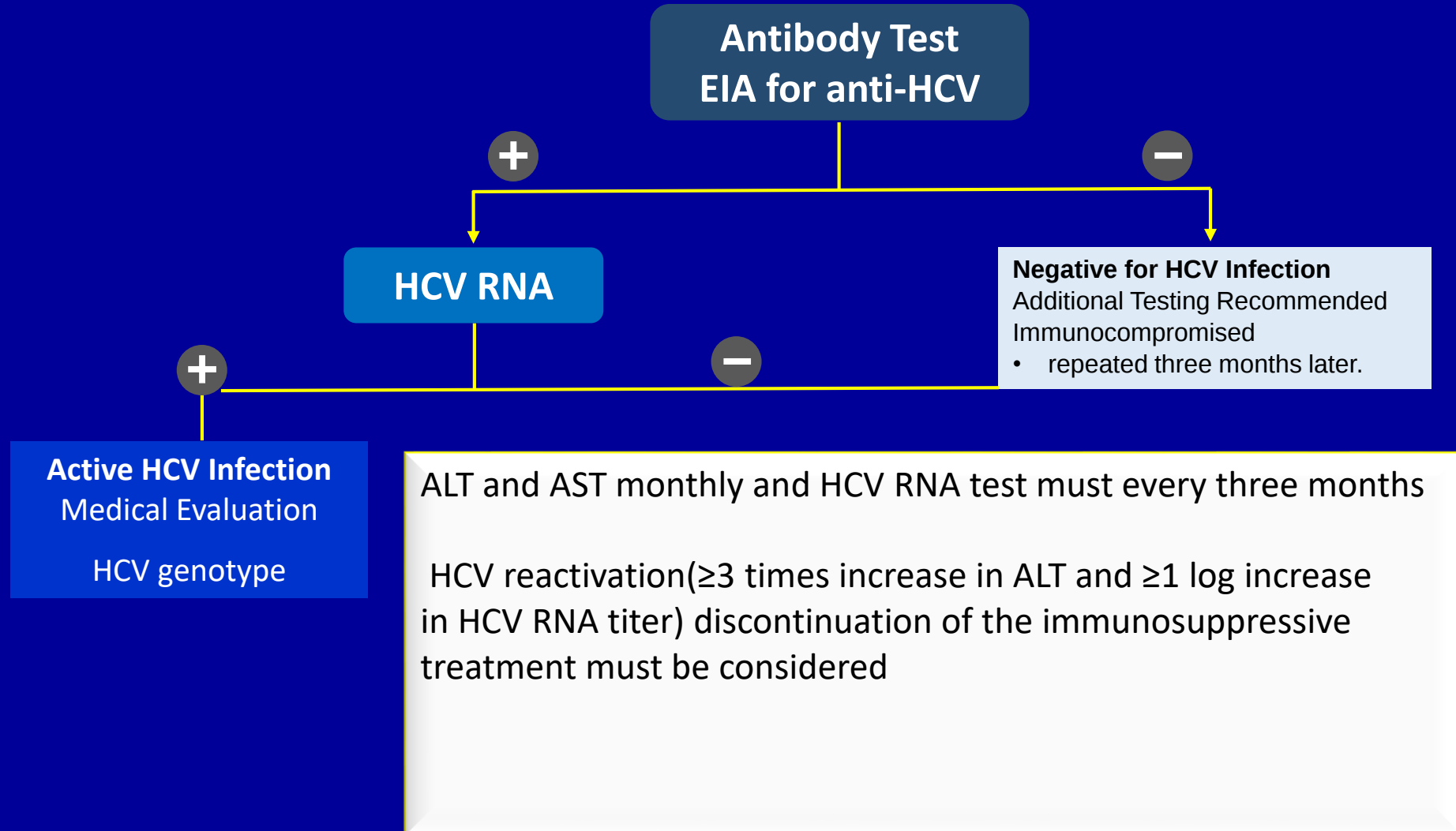


²Treatment period is up to HBsAg becomes negative in the patients with chronic B hepatitis (liver disease), and antiviral treatment should continue 6–12 months after immunosuppressive and/or biological treatment is completed in the patients not having liver disease (12 months in rituximab and ofatumumab treatments)

²If RTX is to be administered, antiviral prophylaxis should be given even if HBV DNA (–)

³HBV DNA is repeated once in 1–6 months (3 months on average)

HCV Diagnostic Algorithm



Biologic therapy in HIV positive patients

- Discussed with an HIV specialist
- CD4+ count >200 cells/mm³ and viral load undetectable
- Combination with highly active anti-retroviral therapy

Malignancy

- Biologic therapies should not be commenced in patients with clinical signs of, or under investigation for, malignancy (BCC excluded)
- Patients should be advised that there is no conclusive evidence for an increased risk of solid tumours or lymphoproliferative disease linked with biologic therapy, but that ongoing vigilance is required

Malignancy

- patients should be advised of the need for preventative skin care, skin surveillance and prompt reporting of new persistent skin lesions
- Anti-TNF therapy is relatively contraindicated in patients who have had prior treatment with >150 psoralen and ultraviolet A (PUVA) and/or >350 ultraviolet B (UVB) phototherapy.

Malignancy

- The timing of commencement of biologic therapy post-malignancy is not fixed and will depend on type and stage of malignancy, risk of metastasis and patient views.
- RTX may be considered as a first-line biologic option in patients with previous malignancy and pre-malignant conditions.

Respiratory and Cardiac problems

- Pre-existing ILD is not a specific contraindication to biologic therapy
- RTX or ABA may be considered a first-line biologic in patients with ILD
- Biologics should be used with caution in patients with class III or IV cardiac failure and previous myocardial infarction

Monitoring on treatment

- Reviewed for drug safety in a specialist department at least every 3-6 months
- Monitoring blood tests (FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 3-6 months (other than TCZ)
- Laboratory monitoring every 4 weeks for neutrophils and ALT/AST (TCZ)
- Blood tests should ideally be in the week before i.v. TCZ, and in the 3 days before every fourth s.c. injection.
- Serum lipids every 3 months (TCZ)
- Serum immunoglobulins(IgG and IgM) checked prior to each cycle of RTX.

Co-morbidity management on treatment

- TB (monitoring on treatment and for at least 6 months after treatment)
- Opportunistic infection
- HIV (close monitoring of viral load and CD4 count)
- Malignancy
- Cardiac problems
- Uveitis (switching ETN to IFX or ADA)
- Multifocal Leukoencephalopathy (PML) *(ABA/RTX)
- Demyelinating disease*(Consider non-anti-TNF biologic)
- Diverticular disease (TCZ) / GI Perforation (TCZ / Tofacitinib) *

* Rechallenge is not recommended

Co-morbidity management on treatment

- Occult or Overt HBV infection (AST/ALT/HBV DNA)
- HCV infection (AST/ALT)
- Respiratory disease/ILD (PFT every 4-6 months)
(RTX or ABA considered in patients with worsening or new ILD)
- Varicella (significant exposure chickenpox or shingles)
VZIG/ Oral aciclovir at 10mg/kg four times a day should be issued if
VZV IgG is negative or <150mIU/ml
- Measles exposure/negative measles IgG
HNIG would be required within three days of exposure

Pregnancy

- Anti-TNF agents fall within the US FDA category B concerning fetal risk
 - Anti-TNF agents can be used during the first half of pregnancy.
 - Stopped before the third trimester (apart from **Certolizumab**)
 - Use of certolizumab can be continued throughout the pregnancy because it does not cross the placenta in significant amounts.
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- **Etanercept** may also be a reasonable alternative because its placental transfer is less than adalimumab or infliximab.

Pregnancy

- Due to the placental transfer of the biologic during the pregnancy there is a potential for an impaired immune response of your infant:
 1. live vaccinations can be administered for 6 months after birth
 2. Inactive vaccinations can be administered in accordance with CDC-recommended guidelines

Breastfeeding

- Breastfeeding by mothers currently treated with anti-TNF alpha biologic treatment regimens is generally considered safe due to the minimal amounts of medication that are present in breast milk and infant gastric digestion.

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