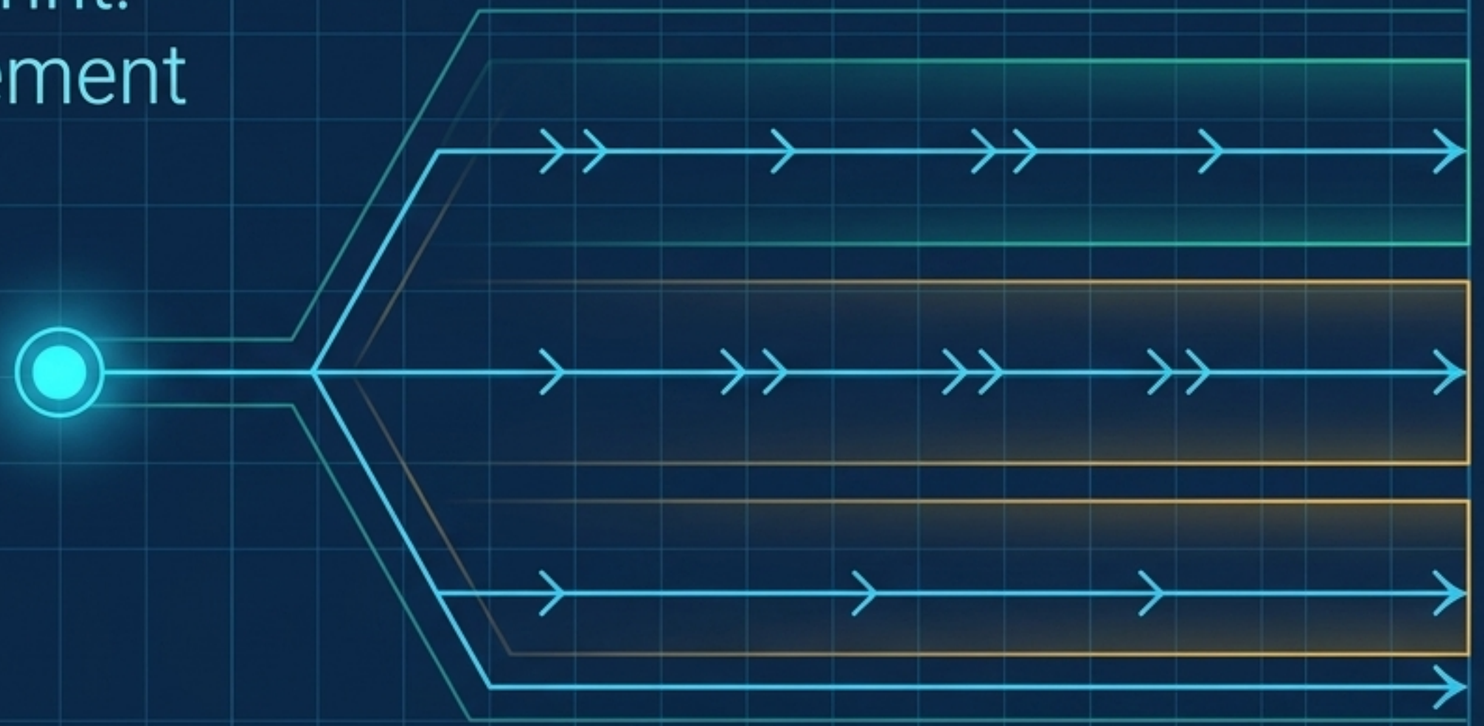
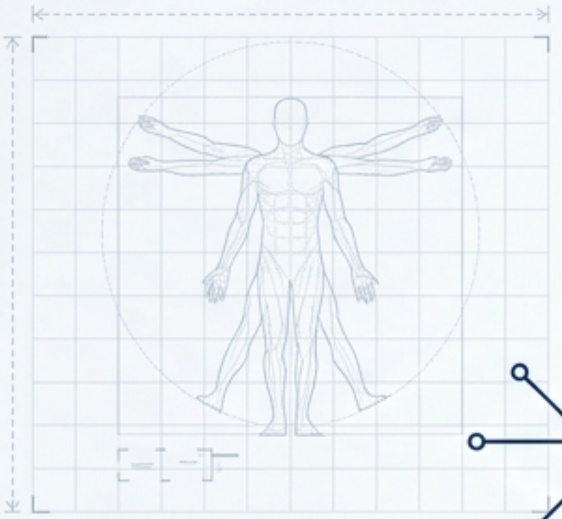
# 2021 ACR Clinical Blueprint: Pharmacologic Management of Rheumatoid Arthritis

A definitive visual translation of the American College of Rheumatology Treatment Guidelines.

From GRADE Methodology to Point-of-Care Algorithms.





## 1. Initiate Treatment

Base decisions on Shared Decision-Making (SDM) and patient comorbidities.

## 2. Monitor Disease Activity

Systematic assessment using validated tools.

## 3. Target Reached?

**Re-evaluate within a minimum of 3 months.**

**No**

## 4. Escalate / Adjust

Adjust to minimize inflammation, prevent joint damage, and mitigate cardiovascular/osteoporosis risk.

**Yes**

**Initial goal:** Low Disease Activity (Conditional preference).
**Ultimate goal:** Remission.

### The Treat-to-Target (TTT) Engine

TTT is **Strongly Recommended** for bDMARD/tsDMARD-naive patients, and **Conditionally Recommended** for patients with prior b/tsDMARD exposure.

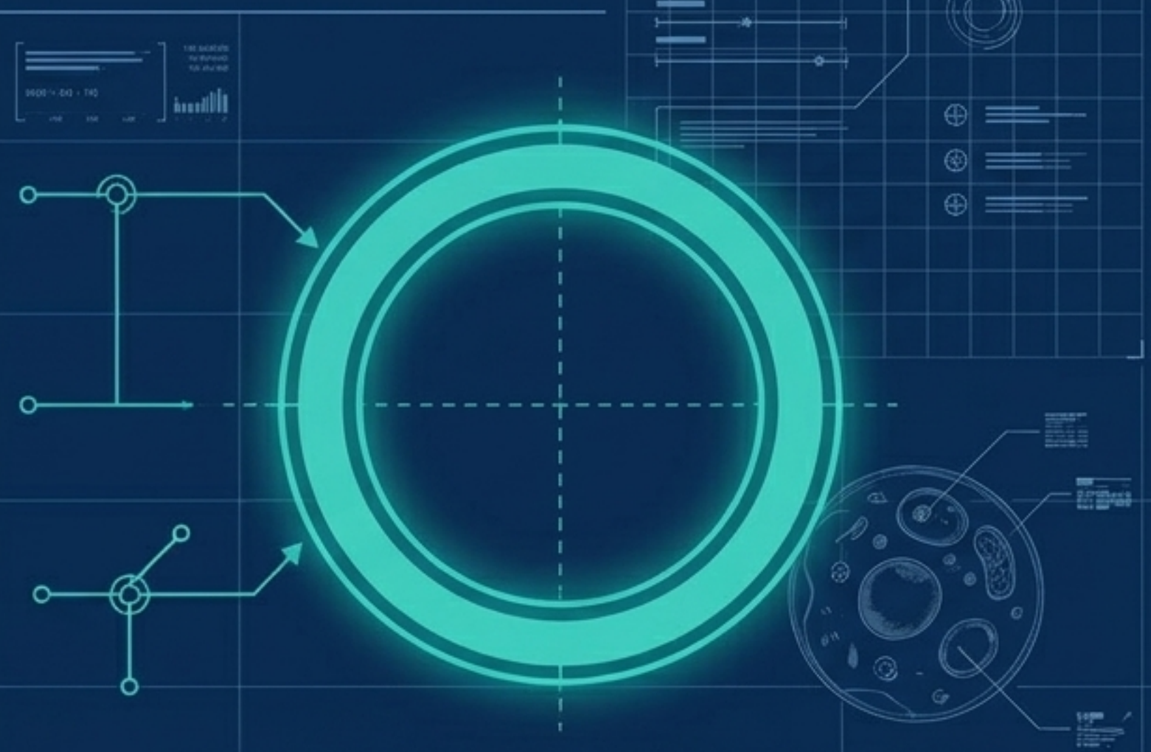
# The Recommendation Weight Ledger

Deciphering the GRADE framework at the point of care.

## STRONG RECOMMENDATION

**Definition:** High confidence that expected benefits favorably balance risks for the vast majority of patients.

**Action:** Standard of care; highly actionable.

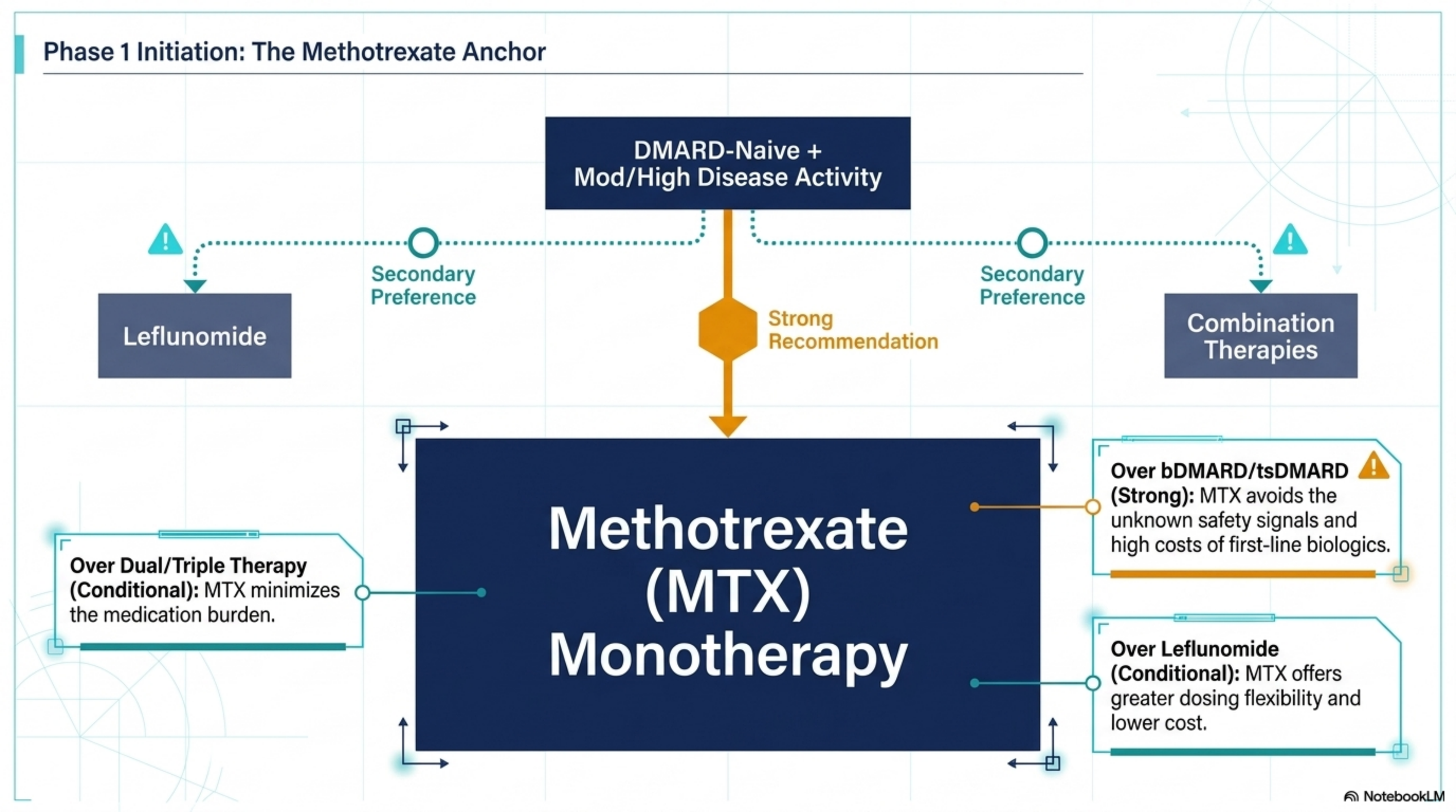


## CONDITIONAL RECOMMENDATION

**Definition:** Lower certainty in evidence, or expected substantial variation in patient values and preferences.

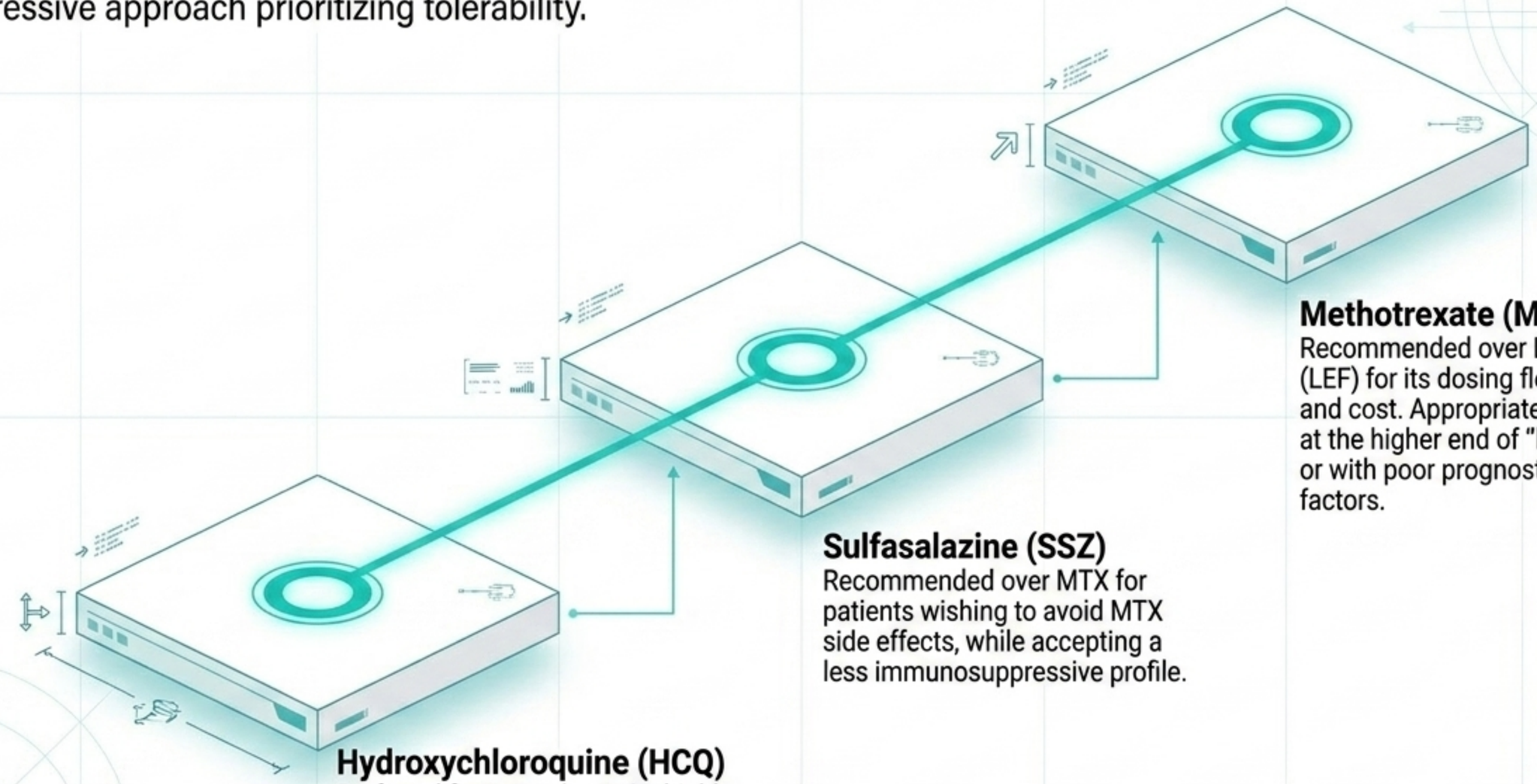
**Action:** Requires nuanced shared decision-making; highly preference-sensitive.

## Phase 1 Initiation: The Methotrexate Anchor



## Phase 1 Initiation: Low Disease Activity

A progressive approach prioritizing tolerability.



**Hydroxychloroquine (HCQ)**
Preferred first step due to its highly favorable risk/tolerability profile in low-activity RA.

**Sulfasalazine (SSZ)**
Recommended over MTX for patients wishing to avoid MTX side effects, while accepting a less immunosuppressive profile.

**Methotrexate (MTX)**
Recommended over Leflunomide (LEF) for its dosing flexibility and cost. Appropriate for patients at the higher end of "low activity" or with poor prognostic factors.

# The Glucocorticoid Squeeze

A systemic philosophical shift to minimize and eliminate steroid exposure


## Short-Term Use (<3 mo)

Initiate csDMARDs without short-term steroids. Limit use to the lowest effective dose for the shortest duration to bridge symptoms.

## Long-Term Use (≥3 mo)

Initiate csDMARDs without longer-term steroids. Significant toxicity universally outweighs benefits.

## Escalation Protocol

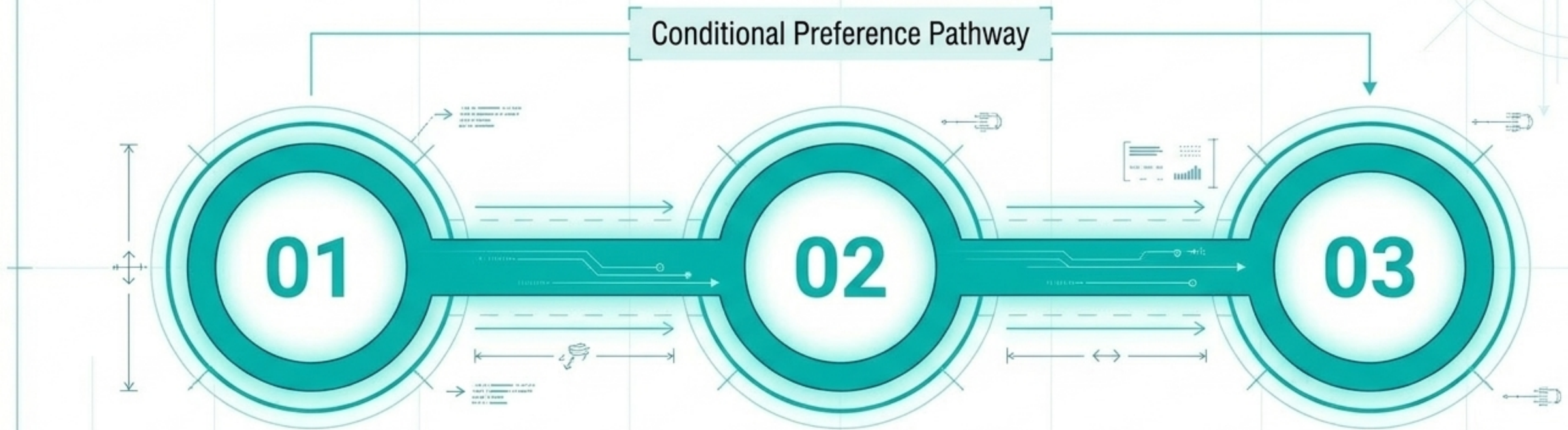
If a patient requires steroids to remain at target, switch/add DMARDs rather than continuing steroids.

## Managing Flares

Switch/add DMARDs over relying on intraarticular (IA) steroid injections alone.

## Phase 2: Maximizing the Methotrexate Anchor

Exhausting MTX utility before escalating to costlier therapies.




### Initiation & Titration

- Start Oral MTX. Escalate to a weekly dose of ≥15 mg within 4 to 6 weeks.

### Managing Intolerance

- If oral MTX is poorly tolerated, do not abandon MTX yet. Interventions:
  - Split oral dose over 24 hours
  - Increase folic/folinic acid
  - Switch to SubQ MTX

### Inadequate Efficacy

If not at target on oral MTX, switch to Subcutaneous (SubQ) MTX before adding or switching to alternative DMARDs.

# Phase 3 Escalation: The Post-MTX Fork

**Patient on maximally tolerated MTX, not at target.**

## Add bDMARD or tsDMARD

- **Rationale:** Prioritizes rapid onset of benefit and improved treatment persistence.
- **Patient Panel Stance:** Strongly favored by patients for fastest possible symptom relief.

## Triple Therapy (Add SSZ + HCQ)

- **Rationale:** Equivalent long-term outcomes to biologics at significantly lower societal cost.
- **Ideal For:** Lower resource settings or patients with specific comorbidities increasing risk of adverse events.

**Note:** If a patient is already on a b/tsDMARD and not at target, switch to a different class of b/tsDMARD rather than cycling within the same class.

# Phase 4 Tapering: De-escalation Protocol

**Prerequisite Gateway: The 6-Month Rule**
Patients MUST be at target (low disease activity or remission) for at least 6 months prior to any tapering.

**Continue all DMARDs** at current dose

**Preferred** (Conditional)

**Dose Reduction** (Lowering dose or increasing interval)

**Conditional** over discontinuation

**Gradual Discontinuation** (Slowly lowering dose before stopping)

**Conditional** over abrupt

~~**Abrupt Discontinuation**~~

**AVOID:** High risk of disease flare and irreversible damage

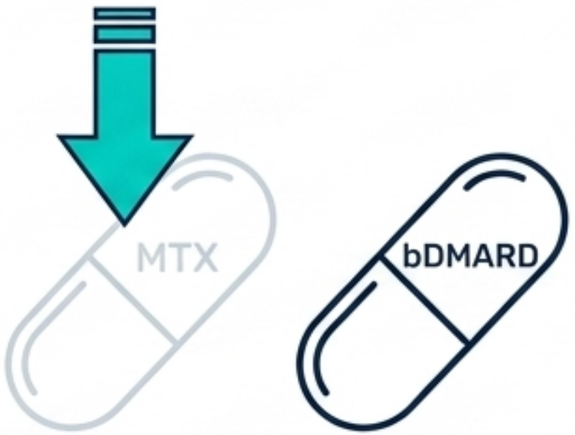
# Tapering Combination Regimens

## Tapering Triple Therapy (MTX + HCQ + SSZ)


Gradually discontinue Sulfasalazine (SSZ) first.

SSZ has **poorer treatment persistence** due to adverse events compared to HCQ.

## Tapering MTX + bDMARD/tsDMARD

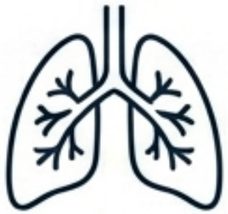



Gradually discontinue Methotrexate (MTX) first.

The b/tsDMARD was added due to prior MTX failure, making the biologic more critical for maintaining disease control.

**Warning:** Some patients on monoclonal antibodies may require ongoing MTX to prevent anti-drug antibody formation.

# The Comorbidity Matrix: Structural & Organ Systems

| Condition | Initiation / Strategy | Progression / Rationale |
| --- | --- | --- |
| **Subcutaneous Nodules**  | Use MTX over alternatives. | If nodules are progressive on MTX, switch to a non-MTX DMARD. |
| **Mild/Stable Pulmonary Disease**  | Continue to use MTX over alternative DMARDs. | MTX remains the anchor; overall risk of worsening lung disease is uncertain, and alternatives also carry lung toxicity risks. |
| **Heart Failure** (NYHA Class III/IV)  | Add a non-TNF b/tsDMARD over a TNF inhibitor. | If HF develops while on a TNF inhibitor, switch to a non-TNF b/tsDMARD. |

# The Comorbidity Matrix: Hepatic Risk Profiles

## Hepatitis B Flowchart

**Patient is Hepatitis B Core Antibody Positive**

- **A** → Initiating **Rituximab** (Any Surface Ag) → ⚠ **Prophylactic Antiviral Therapy (STRONG)**
- **B** → Initiating ANY b/tsDMARD **+ Surface Ag Positive** → ⚠ **Prophylactic Antiviral Therapy (STRONG)**
- **C** → Initiating non-Rituximab b/tsDMARD + Surface Ag **Negative** → ? **Frequent monitoring alone (Conditional)**

## Nonalcoholic Fatty Liver Disease (NAFLD)

**Rule:** MTX is conditionally recommended for DMARD-naive patients ONLY IF they have:

- - Normal liver enzymes
- - Normal LFTs
- - No advanced fibrosis

**Action:** Requires strict 4-8 week monitoring.

# The Comorbidity Matrix: Immunology & Infection

| | |
|---|---|
|  **Previous Serious Infection (within 12 months)** | • **Not at target on MTX?** → Add csDMARDs over b/tsDMARDs **(Conditional).**<br>• **Not at target general?** → Add/switch DMARDs over initiating/escalating glucocorticoids **(Conditional).** |
|  **Nontuberculous Mycobacterial (NTM) Lung Disease** | • **Steroids:** Lowest possible dose, discontinue if possible.<br>• **Escalation:** Add csDMARDs over b/tsDMARDs.<br>• **Biologic choice:** If csDMARDs fail, Abatacept is preferred over other b/tsDMARDs **(Conditional).** |
|  **Immune Disorders** | • **Prev Lymphoproliferative Disorder:** Rituximab preferred over other DMARDs.<br>• **Hypogammaglobulinemia (No infection):** Continue Rituximab if at target over switching classes. |

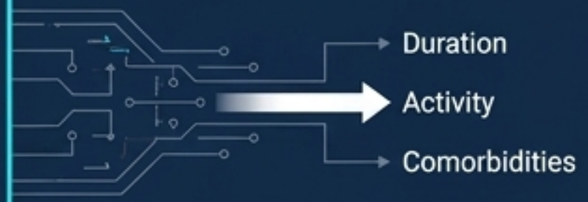
# The 2021 Paradigm Shift

## Moving toward precision algorithms and long-term toxicity mitigation.

### 01

### The Death of “Early vs. Late”

The guidelines abandon treating based on disease duration. Decisions are now driven entirely by current disease activity, prior therapies, and specific patient comorbidities.




### 02

### The Steroid Elimination Imperative

An unprecedented, systemic push to squeeze glucocorticoids out of RA management, recognizing their profound long-term cardiovascular, infectious, and skeletal toxicity.

### 03

### Rapid Escalation & The TTT Engine

A shift away from prolonged conservative measures. Maximize the Methotrexate anchor quickly, and if it fails, prioritize rapid escalation to biologics to secure remission and halt structural damage.