Preoperative Management of Medications for Rheumatologic and HIV Diseases: Society for Perioperative Assessment and Quality Improvement (SPAQI) Consensus Statement

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Abstract

Perioperative medical management is challenging because of the rising complexity of patients presenting for surgical procedures. A key part of preoperative optimization is appropriate management of long-term medications, yet guidelines and consensus statements for perioperative medication management are lacking. Available resources use recommendations derived from individual studies and do not include a multidisciplinary focus on formal consensus. The Society for Perioperative Assessment and Quality Improvement identified a lack of authoritative clinical guidance as an opportunity to use its multidisciplinary membership to improve evidence-based perioperative care. The Society for Perioperative Assessment and Quality Improvement seeks to provide guidance on perioperative medication management that synthesizes available literature with expert consensus. The aim of this consensus statement is to provide practical guidance on the preoperative management of immunosuppressive, biologic, antiretroviral, and anti-inflammatory medications. A panel of experts including hospitalists, anesthesiologists, internal medicine physicians, infectious disease specialists, and rheumatologists was appointed to identify the common medications in each of these categories. The authors then used a modified Delphi process to critically review the literature and to generate consensus recommendations.

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The variety of immunosuppressant medications, biologic medications, antiretrovirals, and nonsteroidal anti-inflammatory drugs (NSAIDs) has grown significantly during the past 2 decades. Decisions about their perioperative management can be challenging as there are often benefits and risks associated with continuation and discontinuation of these medications in the perioperative period. Because guidance is often lacking, the Society for Perioperative Assessment and Quality Improvement (SPAQI) convened a multidisciplinary group of experts in perioperative medicine (hospitalists, anesthesiologists, internal medicine physicians, infectious disease specialists, and rheumatologists) to review available literature and to create consensus recommendations for the perioperative management of medications used for rheumatologic and human immunodeficiency virus (HIV) disease. The guidance of whether to continue or to discontinue these medications is based on the potential harm to the patient, if the medication is held, and the potential impact for the upcoming surgery, if the medication is continued.

Given the implications of therapy discontinuation resulting in potential disease flares, communication with prescribing physicians

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is paramount. Perioperative clinicians should consult the prescribing physician and the surgeon to discuss relevant risks and benefits of therapy interruption in light of the specific clinical situation and the surgical risks. Aside from disease state activity and infection considerations, other factors, such as surgery with or without instrumentation, wound healing, and concomitant medication use, are also important to consider.[1]

METHODS

A modified Delphi method was used to obtain input from a group of experts in perioperative medicine regarding the use of immunosuppressant medications, biologics, NSAIDs, and antiretroviral medications. The Delphi method was selected because of the known lack of high-level evidence related to the perioperative management of these medications. We chose the methodology described by the American Academy of Otolaryngology—Head and Neck Surgery in its 2015 consensus statement, with some modifications necessitated by our topic and participants.[2]

The topic for our consensus statement was chosen by SPAQI leadership, based on a lack of standardized care and evidence related to the management of these medications in the perioperative setting. Consensus group members were selected on the basis of their expertise as well as their grasp of evidence-based medicine. In addition, a group leader was appointed to lead the group through the process, with the approval of the SPAQI executive committee. The final group consisted of 10 experts.

A comprehensive list of immunosuppressant, biologic, NSAID, and antiretroviral medications was identified by literature search of primary and secondary sources. Medications were divided into 4 groups: immunosuppressant medications, biologic medications, antiretroviral medications, and NSAIDs. Group members were asked to consider both the potential benefits and risks of continuing or holding each medication perioperatively.

In the first Delphi round, each group member was asked whether each individual medication should be taken preoperatively. Group members were asked to indicate whether their recommendations for each medications would be "Take," "Hold," or "It depends." Using a 9-point Likert scale, group members were asked to determine the degree to which they supported this recommendation. The Likert scale used the following anchors: 1, strongly agree; 3, disagree; 5, neutral; 7, agree; and 9, strongly agree. Responses were returned to the group leader, who collated the results and distributed the anonymous results back to the group members in a summary form. Definitions for consensus were determined by SPAQI before the start of the process and are summarized in Table 1.

Next, group members were asked to complete a literature search of primary research or summary articles that discussed perioperative management of assigned medications. Results were limited to English-language publications. Both primary (PubMed, package inserts, Micromedex, and others) and secondary (review articles) literature sources were considered. The literature results were summarized and disseminated to the group for review. A second Delphi round was then conducted. Comments were encouraged from the group members to explain differences of opinion on the small minority of medications for which consensus was not reached. The results and comments from the surveys and literature reviews were then discussed in a conference call, and final recommendations were agreed on.

RECOMMENDATIONS

A total of 108 medications were identified by the group. Perioperative considerations and recommendations for each of the 4 groups of medications are presented here as well as in the accompanying tables. Given the lack of high-quality prospective randomized controlled trials, consensus recommendations rely on expert opinion drawn from mostly retrospective, observational studies.

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TABLE 1. Consensus Definition

Category	Mean score		Outliers
Consensus	>7.0	and	≤1
Near consensus	≥6.5	and	≤2
No consensus	<6.5	or	≥3

Immunosuppressant Medications

Methotrexate. Methotrexate competitively inhibits dihydrofolate reductase and interferes with DNA synthesis and repair. In rheumatoid arthritis, methotrexate manifests anti-inflammatory properties through increased local deposits of adenosine and inhibition of interleukin (IL) 6 and 8 production.[3] Concomitant use with other medications that impair kidney function should be cautioned against, especially during the perioperative period (Table 2).

Multiple retrospective and prospective studies have found that continuation of methotrexate perioperatively is not associated with increased risks of infection or impaired wound healing.[4-8] A large randomized trial of 388 patients reported a perioperative infection risk of 2% in those who continued methotrexate vs 15% in patients who stopped the medication perioperatively.[9] Methotrexate interruption can lead to disease flare, which can impede rehabilitation efforts in patients undergoing orthopedic surgery.[10]

Consensus recommendation for methotrexate: *Continue preoperatively, including take on day of surgery (DOS).*

Auranofin. Auranofin is used to treat rheumatoid arthritis in patients with incomplete response to NSAIDs. It suppresses the inflammatory response by inhibiting phagocytosis and release of antibodies and cytotoxic enzymes.[11] No data are available as to its perioperative management, and there are no known anesthetic interactions (Table 2).

Consensus recommendation for auranofin: *Continue preoperatively, including take on DOS.*

Hydroxychloroquine. Hydroxychloroquine interferes with antigen processing in macrophages and other antigen-presenting cells, resulting in down-regulation of the immune response against autoantigens.[12] QT prolongation can occur in patients treated with hydroxychloroquine; therefore, caution should be exercised when other QT-prolonging agents are used perioperatively (eg, volatile anesthetics, methadone, prochlorperazine, and ondansetron, among many others). There is no increased risk of perioperative infections.[4,13,14]

Consensus recommendation for hydroxychloroquine: *Continue preoperatively, including take on DOS.*

Cyclophosphamide. Cyclophosphamide is a potent alkylating agent. Hepatic metabolism leads to the active metabolite phosphoramide mustard and the highly reactive aldehyde acrolein, primarily responsible for cardiac and bladder toxic effects (hemorrhagic cystitis). Cardiac toxic effects, manifested generally as systolic dysfunction and heart failure, are more common after 1 to 10 days after the first dose.[15] Cardiac arrhythmias, both ventricular (QT prolongation—related tachycardias) and supraventricular (atrial fibrillation and flutter), have also been reported with cyclophosphamide use, particularly in patients with underlying heart disease.

Increased risk of infection is a significant concern in patients taking cyclophosphamide as lymphopenia and granulocytopenia peak 7 and 14 days after infusion, respectively.[16] Although cyclophosphamide has been found to have a negative impact on wound healing in animal studies, use of therapeutic doses in human studies has not been reported to impair wound healing.[17] Cyclophosphamide therapy can also cause hyponatremia, probably because of inappropriate antidiuretic hormone release (syndrome of inappropriate secretion of antidiuretic hormone).[18,19]

Cyclophosphamide has many drug-drug interactions, especially with concomitant use with other perioperative medications that induce or inhibit cytochrome P450 enzymes. Concurrent use with anticholinergic agents can increase the risk of hemorrhagic

TABLE 2. Preoperative Recommendations for Immunosuppressant Medications[a]

Medication (brand name)	Preoperative recommendation	Additional considerations	Ancillary testing considerations[b]
Methotrexate[4-10] (Otrexup, Rasuvo, Trexall, Rheumatrex)	Take preoperatively, including on DOS[c]	Affects multiple organ systems (eg, cardiac, renal, pulmonary, hepatic, hematologic) Toxic effects possible with fluctuating renal function	CBC, creatinine, and LFTs
Auranofin[11] (Ridaura)	Take preoperatively, including on DOS[c]	Can decrease white blood cell count	CBC
Hydroxychloroquine[12-14] (Plaquenil)	Take preoperatively, including on DOS[c]	Can prolong QT interval Can cause hypoglycemia, pancytopenia	CBC, ECG
Cyclophosphamide[15-19] (Cytoxan, Neosar)	Hold for 4 weeks	Can cause increased risk of infection, bone marrow suppression, cardiac and bladder toxic effects, SIADH	CBC, electrolytes, and urinalysis
Glucocorticoids[20-27] (Prednisone, Medrol)	Take preoperatively, including on DOS	Associated with hyperglycemia and increased infection risk Chronic use associated with increased postoperative complications including increased infection, therefore should be tapered to lowest dose possible preoperatively	Fasting glucose
Apremilast[28-30] (Otezla)	Take preoperatively, including on DOS[c]	Can cause headache, dizziness, diarrhea, and nausea/vomiting	
Sulfasalazine[29,31,32] (Azulfidine)	Take preoperatively, including on DOS[c]	Concomitant use with NSAIDs associated with increased bleeding	CBC, LFTs, and creatinine
Leflunomide[25,33,34] (Arava)	Take preoperatively, including on DOS	Can cause respiratory infections, headache, rash, and abnormal liver enzymes Drug-drug interactions with several oral antidiabetic agents, which can increase hypoglycemic effect	CBC, LFTs
Mycophenolate[35] (CellCept, Myfortic, MMF)	Take preoperatively, including on DOS for severe SLE Hold for 7 days for nonsevere SLE	Toxic effects can occur if renal function declines postoperatively	CBC, electrolytes, and creatinine
Azathioprine[36-38] (Imuran, Azasan)	Take preoperatively, including on DOS for severe SLE Hold for 7 days for nonsevere SLE	Restart 3-5 days postoperatively as long as there are no issues with wound healing or infection at the surgical site or elsewhere	CBC, LFTs, and creatinine

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TABLE 2. Continued

Medication (brand name)	Preoperative recommendation	Additional considerations	Ancillary testing considerations[b]
Cyclosporine[39-42] (Gengraf, Neoral, Sandimmune)	Take preoperatively, including on DOS for severe SLE Hold for 7 days for nonsevere SLE	Neurotoxic effects (paresthesias, delirium, seizures) and nephrotoxic effects Multiple drug-drug interactions with drugs that inhibit/induce CYP34A (many of which are used in perioperative setting); close monitoring of cyclosporine levels required Restart 3-5 days postoperatively as long as there are no issues with wound healing or infection at the surgical site or elsewhere	CBC, electrolytes, magnesium, glucose, and creatinine
Tacrolimus[25,39,43-45] (Prograf, Astagraf, Hecoria, Protopic, Envarsus)	Take preoperatively, including on DOS for severe SLE Hold for 7 days for nonsevere SLE	Can cause nephrotoxic and neurotoxic effects, QT prolongation, new-onset diabetes, and pure red cell aplasia Multiple drug-drug interactions with drugs that inhibit/induce CYP34A (many of which are used in perioperative setting); close monitoring of tacrolimus levels required Restart 3-5 days postoperatively as long as there are no issues with wound healing or infection at the surgical site or elsewhere	ECG, CBC, electrolytes, magnesium, glucose, and creatinine
Voclosporin (Lupkynis)	Continue cycle uninterrupted and schedule surgery at the end of the cycle	Can cause nephrotoxic and neurotoxic effects, QT prolongation, hypertension Multiple drug-drug interactions with drugs that inhibit/induce CYP34A	ECG, CBC, electrolytes, magnesium, and creatinine

[a]CBC, complete blood count; DOS, day of surgery; ECG, electrocardiogram; LFTs, liver function tests; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SLE, systemic lupus erythematosus.
[b]These considerations pertain to monitoring with long-term therapy and should be applied perioperatively only as dictated by the clinical scenario (not generally required preoperatively).
[c]Not thought to increase risk of infection.

cystitis. Because cyclophosphamide inhibits pseudocholinesterase, the clinical effects of succinylcholine may be prolonged.

Although there are no recommendations for the perioperative management of patients taking cyclophosphamide for rheumatic diseases, it seems reasonable to schedule elective procedures 4 weeks after an intravenous dose to avoid the risk of infection in the setting of neutropenia.

Consensus recommendation for cyclophosphamide: *Hold for 4 weeks before elective surgery.*

Glucocorticoids. Corticosteroids reduce inflammatory cytokine production, activation of T cells, and collagen production; inhibit angiogenesis; and decrease wound tensile strength.[20] Because of increased risk of infection and poor wound healing, concerns about perioperative use of corticosteroids have been raised. In addition, patients who take corticosteroids long term are at increased risk of hypothalamic-pituitary-adrenal axis suppression.

A recently published analysis of more than 14,000 patients from the American College of Surgeons National Surgical Quality Improvement Program reported higher rates of surgical site infection, deep wound infection, wound dehiscence, pneumonia, urinary tract infections, unplanned reintubation, and readmission in patients who were receiving

long-term corticosteroid therapy before hip or knee arthroplasty compared with patients who were not taking corticosteroids long term.[21] In another American College of Surgeons National Surgical Quality Improvement Program study of patients undergoing spinal surgery, the authors reported an increased risk of 30-day postoperative complications including wound dehiscence, deep venous thrombosis, blood transfusion, and mortality.[22]

Based on data from observational studies, the risk of infection is thought to be dose and duration related. Patients taking more than 20 mg of prednisone a day for more than 2 weeks or more than 15 mg/d for a longer time were reported to have increased risk of infection.[23] Another retrospective study of patients with rheumatoid arthritis undergoing total knee or hip arthroplasty detected higher postoperative complications among patients who received higher cumulative doses of corticosteroids (short-term complications increased by 8.4% for every 10-mg increase in glucocorticoid dose).[24]

The 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons (ACR/AAHKS) guideline for the perioperative management of antirheumatic medication in patients with rheumatic disease undergoing elective total hip or total knee arthroplasty suggests tapering corticosteroids to less than 16 mg/d, if feasible, before elective total knee or hip replacement to decrease the risk of infection.[25] However, this should be done under the treating rheumatologist's guidance as tapering of corticosteroids may result in disease flare.

Exogenous use of corticosteroids also suppresses the hypothalamic-pituitary-adrenal axis, which can result in perioperative hemodynamic instability.[26] Patients taking corticosteroid doses of more than 5 mg daily for longer than 4 weeks are considered to be at risk of hypothalamic-pituitary-adrenal axis suppression, and administration of "stress dose" corticosteroids should be considered in high-stress surgical situations.[27]

Consensus recommendation for glucocorticoids: *Continue preoperatively, including take on DOS.*

Apremilast. Apremilast is a phosphodiesterase 4 inhibitor specific for cyclic adenosine monophosphate. Apremilast use results in increased levels of intracellular cyclic adenosine monophosphate, resulting in decreased immune cell activation and decreased release of proinflammatory cytokines. There is no reported evidence that apremilast increases risk of infection or delays wound healing perioperatively as patients planned for elective procedures within 6 to 8 weeks were excluded from the drug trials.[28] It has a short half-life of 6 to 9 hours, and a conservative perioperative management approach would suggest stopping it 2 or 3 days preoperatively.[29,30] However, given the lack of evidence pertaining to increased infection risk as well as no anesthetic interactions, it is the group's decision to recommend continuation of apremilast preoperatively.

Consensus recommendations for apremilast: *Continue preoperatively, including take on DOS.*

Sulfasalazine. Sulfasalazine manifests its anti-inflammatory effect by decreasing immunoglobulin levels and interference with function of T cells.[31,32] There are minimal concerns with wound healing during the perioperative period, and there are no reported anesthesia interactions. Important drug-drug interactions have been reported with concomitant use of NSAIDs, which increases the risk of bleeding. There is little controversy about continuation of this drug in the perioperative period, and 1 article cites a lower incidence of perioperative infection.[29]

Consensus recommendation for sulfasalazine: *Continue preoperatively, including take on DOS.*

Leflunomide. Leflunomide interferes with B-cell and T-cell processes and the intramitochondrial enzyme dihydroorotate dehydrogenase.[33] Its active metabolite interferes with cytokine production in T cells, and its

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TABLE 3. Preoperative Recommendations for Biologic Agents Used to Treat Rheumatologic Disease[a]

Medication (brand name)	Preoperative recommendations	Dosing cycle	When to schedule elective surgery after discontinuation	Additional considerations[b]	Additional testing considerations[c]
TNF-α inhibitors[46-57]					
Adalimumab[d] (Humira, Amgevita, Hulio, Hyrimoz, Idacio, Imraldi)	Hold for an entire dosing cycle	Every 1-2 weeks	Week 3	Can cause neutropenia May cause new onset or worsening of existing heart failure Can cause hepatotoxic effects (infliximab, adalimumab)	CBC, LFTs
Certolizumab[d] (Cimzia)		Every 2 or 4 weeks	Weeks 3 or 5		
Etanercept[d] (Enbrel)		Every 1 week	Week 2		
Golimumab[d] (Simponi, Simponi Aria)		Every 4 weeks (SQ) or Every 8 weeks (IV)	Week 5 (SQ) or Week 9 (IV)		
Infliximab[d] (Remicade, Inflectra, Renflexis)		Every 4-8 weeks	Weeks 5 or 9		
IL-1 inhibitors					
Anakinra[47,56] (Kineret)	Hold for an entire dosing cycle	Daily	Day 2	Modest infectious risk Can cause increased LFT abnormalities	CBC, creatinine, LFTs
Canakinumab[58] (Ilaris)		Every 4 or 8 weeks	Week 5 or 9	Modest infectious risk	
Rilonacept (Arcalyst)		Every 1 week	Week 2	Modest infectious risk	
IL-6 inhibitors[59-65]					
Tocilizumab[d] (Actemra)	Hold for an entire dosing cycle	Every 1 week (SQ) or Every 4 weeks (IV)	Week 2 (SQ) or Week 5 (IV)	Can cause neutropenia, thrombocytopenia, dyslipidemia, and elevated liver enzymes Significantly suppresses inflammatory response, which can mask significant infection postoperatively and delay wound healing	CBC, LFTs
Sarilumab[d] (Kevzara)		Every 2 weeks	Week 3	Can cause increased LFT abnormalities, neutropenia	
IL-17 inhibitors					
Secukinumab[d] (Cosentyx)	Hold for an entire dosing cycle	Every 2 weeks	Week 3	Can cause increased LFT abnormalities, neutropenia	CBC, LFTs
Brodalumab (Siliq)		Every 2 weeks	Week 3	Can cause neutropenia	CBC
Ixekizumab[d] (Taltz)		Every 4 weeks	Week 5		
IL-12/23 inhibitors[47,66]					
Ustekinumab[d] (Stelara)	Hold for an entire dosing cycle	Every 12 weeks	Week 13		
IL-23 inhibitors					
Guselkumab[d] (Tremfya)	Hold for an entire dosing cycle	Every 12 weeks	Week 13		
Risankizumab[d] (Skyrizi)		Every 12 weeks	Week 13		
Costimulation blockade[47]					
Abatacept (Orencia)	Hold for an entire dosing cycle	Every 1 week (SQ) or Every 4 weeks (IV)	Week 2 (SQ) or Week 5 (IV)		
B-cell agents[25,47]					
Rituximab[d] (Rituxan)	Hold for an entire dosing cycle for nonsevere SLE	Every 6 months	Month 7 if nonsevere SLE Month 6 if severe SLE	Ideally hold 6 months preoperatively	CBC, creatinine

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TABLE 3. Continued

Medication (brand name)	Preoperative recommendations	Dosing cycle	When to schedule elective surgery after discontinuation	Additional considerations[b]	Additional testing considerations[c]
Belimumab (Benlysta)	Continue cycle uninterrupted for severe SLE	Every 1 week (SQ) or Every 4 weeks (IV)	Week 2 (SQ) or week 5 (IV) if nonsevere SLE Anytime (SQ) or week 4 (IV) if severe SLE	Can cause neutropenia	CBC, LFTs
Anti-interferon agents					
Anifrolumab (Saphnelo)	Continue cycle uninterrupted	Every 4 weeks (IV)	Week 4		
Janus kinase (JAK) inhibitors[67,68]					
Baricitinib[d] (Olumiant) Tofacitinib[d] (Xeljanz) Upadacitinib[d] (Rinvoq)	Hold for 3 days preoperatively	Daily Daily Daily	Day 4 Day 4 Day 4	Black box warning due to increased risk of myocardial infarction, stroke, or thrombosis Consider perioperative thrombotic prophylaxis Tofacitinib (CYP3A4) and upadacitinib (CYP3A4, CYP3D6) are metabolized through the cytochrome P450 pathway, so if they are coadministered with strong inhibitors of these pathways, dose adjustments may be required. Both tofacitinib and upadacitinib are partially renally excreted. Baricitinib does not have significant liver metabolism and is predominantly cleared unchanged through the kidney	CBC, LFTs, creatinine, ECG

[a]CBC, complete blood count; ECG, electrocardiogram; IL, interleukin; LFTs, liver function tests; SQ, subcutaneous; IV, intravenous; SLE, systemic lupus erythematosus; TNF-α, tumor necrosis factor α.

[b]Biologics can be resumed 14 days postoperatively if there are no issues with wound healing or infection, with the exception of JAK inhibitors, which can be resumed after 3 days.

[c]These considerations pertain to monitoring with long-term therapy and should be applied perioperatively only as dictated by the clinical scenario (not generally required preoperatively).

[d]Increased risk of infections.

action persists up to 2 years after drug cessation, which can result in hepatotoxic effects and drug-drug interactions long after leflunomide is stopped.[33] There are no reported anesthesia interactions.

Although there are conflicting recommendations in the literature, based on variable reported outcomes on postoperative infection risk, guidelines recommend continuation during the perioperative period.[25,34]

Consensus recommendation for leflunomide: *Continue preoperatively, including take on DOS.*

Mycophenolate, Azathioprine, Cyclosporine, Tacrolimus, and Voclosporin. Mycophenolate inhibits lymphocyte purine synthesis and subsequent lymphocyte proliferation and is used to treat numerous autoimmune disorders, including lupus. There are no specific anesthesia interactions, and

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perioperative concerns are usually limited to blood dyscrasias and infections.[35]

The immunosuppressant mechanism of azathioprine is not completely understood, but it is hypothesized to inhibit leukocyte and T-cell proliferation and to promote cell apoptosis.[36] Similarly, there are no specific anesthesia interactions. Data on perioperative management for patients taking azathioprine for rheumatologic disease have been limited to observational studies; however, an increased risk of postoperative infection when azathioprine is continued in patients undergoing orthopedic surgery has not been reported.[37] In patients taking azathioprine for inflammatory bowel disease, its perioperative use was not associated with increased postoperative infection.[38]

Cyclosporine is a calcineurin inhibitor that inhibits the early activation phase of T cells without affecting suppressor T cells or antibody-mediated immunity.[39] Perioperative considerations include several medication interactions. The duration of nondepolarizing muscle relaxants may be prolonged,[40] and systemic lidocaine may have decreased clearance. Effects of benzodiazepines and several narcotics (fentanyl, oxycodone, hydrocodone, morphine, buprenorphine, codeine, tramadol, methadone, and meperidine) may be exaggerated because of inhibition of CYP3A4.[41,42] Use of NSAIDs in patients taking cyclosporine may increase the risk of nephrotoxic effects (Table 2).

Tacrolimus is a potent calcineurin inhibitor that inhibits the first phase of T-cell activation and may suppress humoral immunity.[39] There are several perioperative considerations for patients taking tacrolimus. Tacrolimus is a CYP3A4 substrate, and concomitant use of opioids (buprenorphine, fentanyl, tramadol, methadone), barbiturates, benzodiazepines, dexamethasone, and lidocaine can increase tacrolimus toxicity.[43] Tacrolimus increases the QT interval; therefore, halogenated anesthetics and ondansetron should be used with caution because of risk of arrhythmias. As a potent immunosuppressant, there is also an increased risk for infection.

Voclosporin is a calcineurin inhibitor immunosuppressant approved for treatment of lupus nephritis.[44] Potential adverse effects relevant to the perioperative period include hypertension, increased risk of infection, neurotoxic effects, and acute kidney injury. Voclosporin prolongs the QT interval, and the same considerations as with tacrolimus should be observed.

When used for rheumatologic disease, these 5 agents are prescribed for treatment of systemic lupus erythematosus (SLE). In general, they are reserved for patients with severe SLE (significant renal impairment, neuropsychiatric lupus, cytopenias, or vasculitis). There is sparse perioperative literature and a lack of high-quality data. Other guidelines have used low-quality evidence and expert consensus to guide recommendations for medication management of these agents. Data were extrapolated from single organ transplant patients on similar medication regimens undergoing total knee and joint arthroplasties.[45,46] Despite the increase in postoperative complications in patients who continued these medications, there is concern for disease flare causing significant end-organ damage in patients with severe SLE interrupting therapy.[25] The risk may be less in patients with mild or moderate SLE (skin manifestations, oral ulcers, arthritis).

Consensus recommendation for mycophenolate, azathioprine, cyclosporine, tacrolimus, and voclosporin: *Continue preoperatively, including take on DOS in patients with severe SLE.*

Special consideration for mycophenolate, azathioprine, cyclosporine, and tacrolimus: *Hold for 1 week before procedure in patients with nonsevere SLE.*

Biologic Medications

Tumor Necrosis Factor α Inhibitors. This class of medications inhibits tumor necrosis factor α (TNF-α)—induced inflammation. Independent of perioperative considerations, these medications are associated with an elevated risk of certain infections (tuberculosis and fungal, bacterial, and viral infections) and malignant neoplasms. In

TABLE 4. Preoperative Recommendations for Antiretroviral Medications[a]

Medication—abbreviation (brand name)	Preoperative recommendations	Additional considerations[b]	Ancillary testing considerations[c]
Nucleoside reverse transcriptase inhibitors (NRTIs)[74]			
Abacavir—ABC (Ziagen) Diadenosine—ddI (Videx) Emtricitabine—FTC (Emtriva) Stavudine—d4T (Zerit) Lamivudine—3TC (Epivir) Tenofovir alafenamide—TAF (Vemlidy) Tenofovir disoproxil fumarate—TDF (Viread) Zidovudine or azidothymidine—ZDV or AZT (Retrovir) Abacavir/lamivudine—ABC/3TC (Epzicom/Kivexa) Abacavir/lamivudine/zidovudine—ABC/3TC/AZT (Trizivir) Tenofovir alafenamide/emtricitabine—TAF/FTC (Descovy) Tenofovir disoproxil fumarate/emtricitabine—TDF/FTC (Truvada) Zidovudine/lamivudine—ZDV/3TC (Combivir)	Continue preoperatively	ZVD (AZT) is available in an IV formulation; HIV expert should be consulted if considered All NRTIs have liquid formulations except for TDF and TAF TDF is available in powder form NRTIs do not interact with the hepatic cytochrome P450 system; few significant drug-drug interactions Dosage reduction indicated if impaired postoperative kidney function for FTC, 3TC, TAF, TDF, and AZT	CBC with differential, LFTs, BMP, creatinine clearance, HbA_{1c} (or fasting blood glucose)
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)[75]			
Delavirdine—DLV (Rescriptor) Doravirine—DOR (Pifeltro) Efavirenz—EFV (Sustiva) Etravirine—ETR (Intelence) Nevirapine—NVP (Viramune) Rilpivirine—RPV (Edurant, Rekambys) Doravirine/lamivudine/tenofovir disoproxil fumarate—DOR/3TC/TDF (Delstrigo) Efavirenz/Emtricitabine/tenofovir disoproxil fumarate—EFV/FTC/TDF (Atripla) Rilpivirine/emtricitabine/tenofovir alafenamide—RPV/FTC/TAF (Odefsey) Rilpivirine/emtricitabin/tenofovir disoproxil fumarate—RPV/FTC/TDF (Complera)	Continue perioperatively	NNRTIs except for DOR have long half-lives; if a prolonged NPO period is expected, the patient's HIV provider should be alerted well in advance of surgery to avoid effectively single-drug therapy with the risk of resistance Combination tablets may need to be switched to the individual drugs for appropriate dosing of the NRTIs NVP tablets should never be crushed; available in suspension EFV capsule can be opened; tablet should not be crushed RPV requires acid for absorption; if NPO requiring acid blockers postoperatively, a change in ART should be considered preoperatively RPV is available as injectable formulation but is approved to be used only with the integrase inhibitor cabotegravir Varied drug-drug interactions with the cytochrome P450 system, which reduces the effectiveness of several important drugs used perioperatively, including fentanyl, hydrocodone, oxycodone, tramadol, and midazolam Prolongs QT interval; drug-drug interactions with other medications that also prolong QT can result in arrhythmias	ECG, CBC with differential, LFTs, BMP, creatinine clearance, HbA_{1c} (or fasting blood glucose)

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TABLE 4. Continued

Medication—abbreviation (brand name)	Preoperative recommendations	Additional considerations[b]	Ancillary testing considerations[c]
Protease inhibitors[76]			
Amprenavir—APV (Agenerase) Atazanavir—ATV (Reyataz) Darunavir—DRV (Prezista) Fosamprenavir—FPV (Lexiva) Indinavir—IDV (Crixivan) Nelfinavir—NFV (Viracept) Ritonavir—RTV (Norvir) Saquinavir—SQV (Invirase) Tipranavir—TPV (Aptivus) Atazanavir/cobicistat—ATV/c (Evotaz) Atazanavir/ritonavir—ATV/r Darunavir/cobicistat—DRV/c (Prezcobix) Darunavir/ritonavir—DRV/r Darunavir/cobicistat/emtricitabine/tenofovir alafenamide—DRV/c/FTC/TAF (Symtuza) Lopinavir/ritonavir—LPV/r (Kaletra)	Continue preoperatively	Dose adjustment is not required for renal insufficiency Combination tablets may need to be switched to the individual drugs for appropriate dosing of the NRTIs Hypertriglyceridemia, hyperglycemia, increased LFT abnormalities Strong inhibitors of hepatic CYP3A4; important drug-drug interactions, which prolong effects of several opioids, benzodiazepines, and dexamethasone Drug-drug interaction with calcium channel blockers and beta blockers; increases PR prolongation and risk for bradycardia, hypotension, and arrythmias Prolongs QT interval; increased risk with drug-drug interactions when concomitantly used with sevoflurane and several antiemetic agents (ondansetron, prochlorperazine, promethazine, droperidol) Dose adjustment of many drugs is required if a patient is taking a protease inhibitor; consider pharmacist assistance Atazanavir requires acid for absorption; if NPO requiring acid blockers postoperatively, a change in ART should be considered preoperatively Drug-drug interactions with H_2 blockers, omeprazole, and pantoprazole	ECG, CBC with differential, LFTs, BMP, creatinine clearance, HbA_{1c} (or fasting blood glucose)
Integrase inhibitors[74]			
Cabotegravir—CAB (Vocabria) Dolutegravir—DTG (Tivicay) Elvitegravir—EVG (Vitekta) Raltegravir—RAL (Isentress) Bictegravir/emtricitabine/tenofovir alafenamide—BIC/FTC/TAF (Biktarvy) Cabotegravir/rilpivirine—CAB LA/RPV (Cabenuva) Dolutegravir/abacavir/lamivudine—DTG/ABC/3TC (Triumeq) Dolutegravir/lamivudine—DTC/3TC (Dovato) Dolutegravir/rilpivirine—DTG/RPV (Juluca) Elvitegravir/cobicistat[d]/emtricitabine/tenofovir alafenamide—EVG/c/FTC/TAF (Genvoya) Elvitegravir/cobicistat[d]/emtricitabine/tenofovir disoproxil fumarate—EVG/c/FTC/TDF (Stribild)		Integrase inhibitors do not require any dosage reduction with renal insufficiency Combination tablets may need to be switched to the individual drugs for appropriate dosing of the NRTIs with renal insufficiency; not all integrase inhibitors are available as individual medications Raltegravir exists in a chewable tablet that can be crushed or administered through a feeding tube Elvitegravir (EVG) metabolized by CYP34A; drug-drug interactions more likely	ECG, CBC with differential, LFTs, BMP, creatinine clearance, HbA_{1c} (or fasting blood glucose)

Continued on next page

TABLE 4. Continued

Medication—abbreviation (brand name)	Preoperative recommendations	Additional considerations[b]	Ancillary testing considerations[c]
CD4 entry inhibitors[74]			
Enfuvirtide—ENF (Fuzeon) Fostemsavir—FTR (Rukobia) Maraviroc—MVC (Selzentry)	Continue preoperatively	No dose adjustment needed with renal insufficiency MVC and FTR are strong inhibitors of hepatic CYP450 MVC has an oral liquid formulation MVC is associated with increased risk of myocardial infarction/ischemia, particularly in patients with postural hypotension, with underlying heart disease, or taking antihypertensive agents FRT can cause prolonged QT interval (particularly with higher doses) or when given with drugs that affect CYP3A substrates Drug-drug interactions with other medications that also prolong QT	
CD4 postattachment inhibitor[74]			
Ibalizumab (Trogarzo)	Continue preoperatively Discuss plan for surgery with HIV provider	No dose adjustment needed with renal insufficiency Given IV every 2 weeks; high risk of resistance if patient NPO for >24 hours perioperatively and receiving monotherapy Can be administered early to prevent challenges with administration during hospitalization	

[a]ART, antiretroviral therapy; BMP, basic metabolic panel; CBC, complete blood count; ECG, electrocardiogram; HbA_{1c}, hemoglobin A_{1c}; HIV, human immunodeficiency virus; IV, intravenous; LFTs, liver function tests; NPO, nil per os.

[b]Many antiretroviral drugs will not be on a hospital formulary and patients should be asked to bring their own supply or the pharmacy should be alerted to procure needed medications.

[c]These considerations pertain to monitoring with long-term therapy and should be applied perioperatively only as dictated by the clinical scenario (not generally required preoperatively).

[d]Cobicistat is not an antiviral agent; it is used for its inhibitory effects (a potent inhibitor of CYP450-CYP3A) to increase systemic exposure of once-daily atazanavir or darunavir. Cobicistat has many drug-drug interactions because of the CYP450-CYP3A inhibition.

addition, because TNF-α plays a critical role in the inflammatory cell recruitment needed for tissue repair, TNF-α inhibitors have been associated with impaired or delayed wound healing.

Studies have had mixed results for infectious complications when these medications are continued perioperatively; some have reported a modestly elevated risk, and others have found no increased risk of wound infection.[38,47-50] One large retrospective review suggested that it may be safe from an infection standpoint for patients to continue the TNF-α inhibitors infliximab, adalimumab, and etanercept perioperatively for low-risk operations but noted that higher risk surgeries require a case-by-case approach.[51] A randomized controlled trial of more than 200 patients with hidradenitis suppurativa described no difference in infection or wound healing outcomes in patients taking adalimumab vs placebo.[52] One small prospective randomized trial of patients taking TNF-α inhibitors perioperatively in foot and ankle surgery did not report an elevated risk for infectious complications.[53] When TNF-α inhibitors are taken in combination with other immunomodulators perioperatively, there does appear to be an increased risk for perioperative infection.[54,55] Whereas some authors have focused on the type of surgery (ie, classification of surgery as low, moderate, or high risk) to determine whether TNF inhibitors should be continued or held,[56,57] many professional societies have grouped all surgical procedures together and recommended discontinuation of TNF-α inhibitors for a period of between 3 and 5 half-lives before surgery.[51] The 2017 ACR/AAHKS guideline

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advises holding of TNF-α inhibitors before surgery based on drug half-life, with typical holding periods usually being a number of weeks before the surgical date, a recommendation supported in its recently published 2022 update.[25,58] Similarly, the 2019 British Society for Rheumatology guidelines suggest stopping TNF-α inhibitors.[59] Our review of the available literature and clinical experience lead us to similar recommendations as those of the ACR/AAHKS and British Society for Rheumatology guidelines.

Consensus recommendation for TNF-α inhibitors: *Hold for an entire dosing cycle before elective surgery* (Table 3).

Interleukin Inhibitors. Anakinra, an IL-1 receptor antagonist, and canakinumab, an IL-1 antibody (Table 3), have modest anti-inflammatory activity relative to TNF-α inhibitors. Data informing the perioperative management of these agents are sparse, but as with the other biologic agents, the primary concerns are increased risk of infection and impaired wound healing. One review of perioperative management of rheumatoid arthritis noted a lack of clear evidence on anakinra perioperatively, and the authors' expert opinion was for anakinra to be continued perioperatively for low-risk procedures and held 24 to 48 hours for moderate- to high-risk surgical procedures.[57] Other authors have advised holding of anakinra for 24 to 48 hours before all surgical procedures.[48]

A large randomized controlled trial of canakinumab in patients with past myocardial infarction, although not in the perioperative setting, revealed that compared with placebo, canakinumab was associated with a significantly lower rate of recurrent cardiovascular events. However, patients in the canakinumab group had a higher incidence of fatal infection and sepsis as well as a reduction in platelet counts, with no increase in bleeding risk.[60] We could find no data or recommendations for perioperative management of canakinumab.

The IL-6 receptor inhibitors (tocilizumab, sarilumab) interfere with IL-6—mediated cellular signaling, thus inhibiting T-cell activation, induction of immunoglobulin secretion, and initiation of hepatic acute phase protein synthesis[61] (Table 3). Whereas tocilizumab is associated with an increased risk for infections in general,[62,63] limited data suggest no increase in postoperative infections after joint surgery.[64,65] Delayed wound healing has been reported in foot and ankle surgery and spine surgeries in patients taking tocilizumab.[66] One small retrospective study also associated tocilizumab with increased blood loss with total knee arthroplasty surgery.[67] The ACR/AAHKS recommendations are to hold the medication for a defined period before surgery, depending on dosing route.[25,58] Evidence guiding sarilumab therapy specifically during the perioperative period is lacking.

The IL-17 inhibitors (secukinumab, ixekizumab) block the effects of IL-17, thought to be a key mediator of cell-mediated cytotoxicity in a number of rheumatologic conditions (Table 3). There are no data guiding perioperative management; however, concerns are similar to those of other biologic agents (infectious risk and poor wound healing).

Ustekinumab is a unique human monoclonal antibody that binds the p40 subunit shared by IL-12 and IL-23 and functions to inhibit the proinflammatory effects of these 2 cytokines. In a study of patients with Crohn disease (its other indication) receiving ustekinumab and undergoing abdominal surgery, there was no increase in early or late postoperative wound infections.[68] Other studies that have examined various biologic agents perioperatively, including ustekinumab, have contained sample sizes of ustekinumab that were too small for useful conclusions to be drawn.[48]

Monoclonal antibodies that target IL-23 (guselkumab) are directed against the p19 subunit of IL-23, and inhibition of this pathway results in blockage of proinflammatory cytokines. No data are available to guide perioperative management of these agents.

Consensus recommendation for all IL inhibitors: Hold for an entire dosing cycle before elective surgery (Table 3).

Selective T-Cell Costimulation Blocker. Abatacept is classified as a selective costimulation modulator that inhibits T-cell activation by binding to CD80 and CD86 on antigen-presenting cells. One review of biologic agents specifically advised that abatacept should be held for 25 days before surgical procedures, largely because of infection risks.[48]

Consensus recommendation for abatacept: Hold for an entire dosing cycle before elective surgery (Table 3).

B-Cell Agents. Rituximab depletes CD20-positive B cells, and belimumab inhibits the activity of B cells through its anti—B lymphocyte stimulator protein effects. Both decrease antibody production, decreasing T-cell activation and inhibiting cytokine production. Rituximab depletes B cells for up to 6 months after a dose, and 1 review suggested that surgery should be postponed until 100 days have passed since the last infusion.[48] The ACR/AAHKS guideline supports holding of rituximab for 4 to 6 months before a planned elective procedure.[25,58] Data are lacking on the risks of belimumab and surgery. A tailored approach is suggested in the 2022 ACR/AAHKS update with regard to scheduling elective surgery during or after a dosing cycle of B-cell agents based on lupus severity, and it is our writing group's decision to support similar recommendations.[58]

Consensus recommendation for B-cell agents: *Hold for an entire dosing cycle before elective surgery for patients with nonsevere SLE* (Table 3).

Special consideration for B-cell agents: *Continue cycle uninterrupted and schedule elective procedure right before the end of the cycle for severe SLE* (Table 3).

Anti-Interferon Agents. Anifrolumab is a human immunoglobulin G1 κ monoclonal antibody that binds with high affinity to the type 1 interferon receptor. It is approved for treatment of moderate to severe systemic lupus.[69] The main perioperative consideration is the increased risk of pulmonary infections; there are no described anesthetic interactions.

Consensus recommendation for anti-interferon agents: Continue cycle uninterrupted and schedule elective procedure right before the end of the cycle.

Janus Kinase Inhibitors. Many cytokines (interferons, interleukins, and colony-stimulating factors) signal through the Janus kinase (JAK) enzyme pathway. A systematic review and meta-analysis of nonsurgical patients receiving tofacitinib has found a clear elevated risk of infections.[70] In addition to infection, venous and arterial thromboembolism is a known potential adverse event associated with JAK inhibitors that is relevant in the perioperative period.[71] The half-life of these medications is short, and they are dosed daily; it is not clear how long the immunosuppressant effect is present.

The ACR/AAHKS guideline as well as the British guideline suggests holding tofacitinib for 7 days; however, recent data point out the risk of disease flare during prolonged discontinuation.[25,71] Given the short half-lives of JAK inhibitors, the group's decision is to recommend discontinuation for a shorter time, which is supported in the updated 2022 ACR/AAHKS guideline.[58]

Consensus recommendation for JAK inhibitors: *Hold for 3 days before elective surgery.*

Antiretroviral Medications

Antiretroviral therapy (ART) has transitioned HIV infection from an illness that predictably led to a hastened death to a chronic and often easily treatable, albeit noncurable, disease.[72,73] Several common principles guide all classes of ART in the outpatient as well as in the perioperative setting.

The first principle is that ideally, patients should have undetectable viral loads before proceeding with elective surgery. An undetectable viral load before surgery decreases the risk of postoperative complications[74] and minimizes the possibility of nosocomial transmission to others through a blood or body fluid exposure.[75]

A second general principle of ART is that once treatment is started, it should be

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TABLE 5. Preoperative Recommendations for Nonsteroidal Anti-inflammatory Drugs[a]

Medication (brand name)	Preoperative recommendations	Half-life, hours	Additional considerations
Nonselective COX-1/COX-2 inhibitors[77-85]			
Diclofenac (Cataflam, Voltaren-XR, Dyloject, Cambia, Zipsor, Zorvolex)	Hold for 7 days	2-3	Could hold for 1 day
Diflunisal (Dolobid)		8-12	Could hold for 3 days
Etolodac (Lodine)		7-11	Could hold for 2 days At a daily dose of 600 to 800 mg, it is relatively COX-2 selective and could be continued in the absence of high bleeding risk surgery
Fenoprofen (Nalfon)		3	Could hold for 1 day
Flurbiprofen[b] (Ansaid, Ocufen, Strepfen)		7-8	Could hold for 2 days
Ibuprofen (Brufen, Advil, Motrin, Nurofen)		2-3	Could hold for 1 day
Indomethacin[b] (Indocin, Indocid)		4-5	Could hold for 1 day Potent inhibitor of renal prostaglandin synthesis
Ketoprofen[b] (Orudis, Oruvail)		2-4	Could hold for 1 day
Ketorolac[b] (Toradol)		6	Could hold for 1 day
Meloxicam (Mobic)		15-20	Could hold for 4 days At a daily dose of 7.5 mg, it is relatively COX-2 selective (5- to 50-fold) and could be continued in the absence of high bleeding risk surgery
Nabumetone (Relafen)		26	Could hold for 6 days At a daily dose of ≤1000 mg/d, it is relatively COX-2 selective
Naproxen[b] (Aleve, EC Naprosyn, Anaprox, Anaprox DS, Naprosyn, Naprox Sodium, Naproxen EC, Naproxen SR, Naprelan, Menstridol)		12-17	Could hold for 4 days
Oxaprozin (Daypro)		36-92	Could hold for 10 days
Piroxicam[b] (Feldene)		50	Could hold for 10 days Daily doses ≥20 mg increased risk of serious gastrointestinal complications
Salasate (Mono-Gesic, Salflex, Disalcid, Salsitab)		1	Could hold for 1 day Does not interfere with platelet function, gastrointestinal bleeding Nephrotoxicity is rare
Sulindac (Clinoril, Sunil)		16-18	Could hold for 4 days Can cause reversible LFT abnormalities
Tolmetin[b] (Tolectin)		2-6	Could hold for 2 days
Selective COX-2 inhibitors[86-91]			
Celecoxib (Celebrex)	Continue preoperatively	11	No effect on platelet function

[a]COX, cyclooxygenase; LFT, liver function test.
[b]More COX-1 selective.

continued unless there is a serious complication of treatment.[76] Patients are generally educated to never stop part of their ART program; they should either take all or stop all of the ART drugs. This is important because ART treatment involves a

combination of agents targeting different points of the virus's life cycle and should be fully suppressive to prevent development of resistance.[5] This principle is important to remember in the perioperative setting, in which holding 1 or more of these drugs might increase the risk of increased viral load or the development of drug resistance.

A third principle is that patients receiving coformulated ART should be instructed to bring their own ART pills to the hospital in the event that their ART is not on the formulary or may not be available. Hospitals may prefer individual agents to coformulated products, which is advantageous should there be a need to adjust dosing for renal or hepatic insufficiency.

Clinicians should ensure that patients continue a fully suppressive ART program uninterrupted during the perioperative period. Regimen changes may be anticipated if patients will be unable to take medications by mouth for a period beyond a few days or in the event of surgical complications, when a patient is unable to take the usual ART.[6] In these cases, it is best for an HIV expert familiar with ART resistance patterns to be involved in the perioperative management. Similarly, for patients for whom combination medications need to be switched to individual components (see later) or oral formulations substituted for powder or intravenous preparations, an HIV expert needs to be consulted as well.

Nucleoside reverse transcriptase inhibitors (NRTIs) inhibit viral replication through competitive inhibition of HIV reverse transcriptase and premature DNA chain termination (Table 4). Given the risk of lactic acidosis, propofol infusion may be avoided in patients treated with NRTIs perioperatively.[77] Otherwise, NRTIs have few significant drug-drug interactions and unlike many other ART medications do not interact with the hepatic cytochrome P450 system.

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) bind to HIV-1 reverse transcriptase and induce a conformational change that limits the activity of the enzyme. Important perioperative considerations are detailed in Table 4. Because NNRTIs are metabolized through the hepatic cytochrome P450 system, they have variable drug-drug interactions relevant in the perioperative period. Importantly, coadministration of NNRTIs with several opioid and benzodiazepine medications used perioperatively (eg, fentanyl, oxycodone, hydrocodone, tramadol, midazolam) can result in reduced levels of these medications and subsequent reduced effectiveness of the intended sedative and pain-reducing effects.[78] Several of these medications also prolong the QT interval and, when coadministered with other QT-prolonging medications, can result in arrhythmias. When coadministered with calcium channel blockers, NNRTIs may result in significantly reduced effectiveness of the calcium channel blockade.

Protease inhibitors interrupt the viral maturation process by competitively inhibiting the enzyme that cleaves HIV polyprotein chains into functional proteins, resulting in noninfectious virions. Protease inhibitors are strong inhibitors of CYP3A4, which results in significant drug-drug interactions to be aware of in the perioperative setting. Particularly, patients who are taking protease inhibitors will have prolonged effects from several opioid medications and benzodiazepines, leading to slower recovery from anesthesia, increased sedation, and respiratory depression.[79] Use of lower doses of analgesics and benzodiazepines, with titration to effect, should be considered because of slower metabolism of these agents. Protease inhibitors also prolong the QT interval and can increase the risk of significant arrhythmias when they are given with other QT-prolonging medications (eg, sevoflurane, ondansetron, prochlorperazine, promethazine, droperidol). Several calcium channel and beta blockers are also affected by drug-drug interactions with protease inhibitors, which increases the availability of these agents, resulting in prolonged PR interval, bradycardia, hypotension, and arrhythmias. The use of acid suppression medications, including some proton pump inhibitors and H_2 blockers, in patients taking protease inhibitors can increase the risk of protease inhibitor toxicity. Protease inhibitors can potentiate the effect of the corticosteroids

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and cause muscle weakness and enhanced adverse effects.

Integrase inhibitors block the integration of reverse transcribed HIV DNA into the chromosomes of cells. If renal impairment is considered to be likely postoperatively, one should consider changing to a fully suppressive program of individual ART components, under the supervision of an HIV specialist. Integrase inhibitor concentrations can be decreased by polyvalent cation—containing antacids and supplements.

Most protease inhibitors and some integrase inhibitors are administered in combination with other agents (pharmacokinetic enhancers) that boost plasma concentrations by prolonging half-lives, increasing maximum and trough concentrations, thus improving efficacy. Drugs in this class include cobicistat, which has no antiviral activity, and ritonavir. Although ritonavir as a protease inhibitor has activity against HIV, it is used only at low dose to enhance other protease inhibitors.

Pharmacokinetic enhancement is based on strong inhibition of the hepatic cytochrome P450 system, specifically CYP34A. Therefore, it affects many perioperatively administered drugs, including anesthetic agents, such as neuromuscular blockers and analgesics. As with the protease inhibitors, it should be anticipated that patients may be slow to recover from anesthesia and may require longer monitoring for respiratory adverse events. One advantage is that pain control may be accomplished with lower doses of analgesics.

Entry inhibitors interfere with viral binding, membrane fusion, and internalization, which prevents HIV infection of CD4 T cells, thus blocking the first step in the viral life cycle. Use is uncommon and limited to treatment-experienced patients with drug-resistant virus. As hospitals are unlikely to stock many of these, patients should be advised to bring their own supply to avoid therapy interruption.

Ibalizumab is a monoclonal antibody that blocks HIV-1 entry into CD4 cells and is the only currently approved CD4-directed post-attachment inhibitor. It is given as an intravenous infusion every 2 weeks and used only for treatment-experienced patients with resistant virus. Resistance to ibalizumab develops with monotherapy. If a patient is expected to be NPO for more than 24 hours perioperatively, the HIV provider should be involved with creating an appropriate perioperative ART plan.

Consensus recommendation for HIV agents: *Continue preoperatively, including take on DOS.*

Nonsteroidal Anti-inflammatory Drugs

The NSAIDs are a heterogeneous class of medications that inhibit the cyclooxygenase (COX) enzymes, thereby interfering with the synthesis of prostaglandins that promote inflammation, pain, and fever. COX has 2 isoforms: COX-1, responsible for gastrointestinal cytoprotection and platelet aggregation; and COX2, expressed selectively and inducible by cytokines and inflammatory tissues producing prostaglandins involved more with inflammation and pain.[80]

All NSAIDs inhibit COX-1 and COX-2 in differing ratios (Table 5). Concerning adverse effects like surgical site bleeding, renal injury, and cardiovascular events are traditionally associated with the inhibition of COX-1. These risks are minimized with COX-2 inhibitors.[29,81,82] However, the literature reporting harmful perioperative NSAID adverse effects is inconsistent and with mixed results at best. In general, postoperative bleeding rates and rates of anastomotic leak with colorectal surgery do not appear to be significantly higher when NSAIDs are used postoperatively as described in multiple meta-analyses.[83-85] Study data of the negative impact on tendon and bone healing are largely in vitro and animal based.[83,86-88]

The inducible expression of COX-2 with surgical trauma is intriguing when one considers the pathophysiologic mechanism of postoperative pain. Nerve endings are stimulated directly or sensitized by inflammatory mediators released by traumatized tissue after injury or surgery, thereby inducing primary and secondary hyperalgesia.[83,89] Although the role for preoperative and postoperative use of these medications to dampen the changes induced by pain ("preemptive analgesia") is compelling, the literature is

inconclusive.[90] Nonetheless, celecoxib is increasingly incorporated in perioperative protocols aimed at reducing total opioid use, improving functional recovery and pain scores as part of a multimodal analgesia plan. However, most studies are not powered to evaluate adverse effects as a primary outcome.[87,91-93] The COX-2 inhibitors have minimal effects on coagulation, and this makes them attractive in the surgical population.[94]

Consensus recommendation for COX-1 inhibitors: *Hold COX-1 inhibitors for 7 days before surgery.*

Consensus recommendation for COX-2 inhibitors: *Continue preoperatively, including take on DOS.*

CONCLUSION

Perioperative medication management is a critical part of optimal care of surgical patients. Literature to support best practices in this area remains sparse, and perioperative decision-making is primarily guided by knowledge of medication mechanisms of action and adverse profiles. Summarized in Tables 2 to 5, this multidisciplinary expert consensus statement provides recommendations for perioperative management balancing risk of disease flare and postoperative infections (immunosuppressant and biologic medications), disease control and minimizing risk of resistance (HIV medications), and pain control vs risk of bleeding for NSAIDs.

POTENTIAL COMPETING INTERESTS

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Abbreviations and Acronyms: **ACR/AAHKS,** American College of Rheumatology/American Association of Hip and Knee Surgeons; **ART,** antiretroviral therapy; **CBC,** complete blood count; **COX,** cyclooxygenase; **DOS,** day of surgery; **HIV,** human immunodeficiency virus; **IL,** interleukin; **JAK,** Janus kinase; **LFT,** liver function test; **NNRTI,** nonnucleoside reverse transcriptase inhibitor; **NRTI,** nucleoside reverse transcriptase inhibitor; **NSAID,** nonsteroidal anti-inflammatory drug; **SLE,** systemic lupus erythematosus; **SPAQI,** Society for Perioperative Assessment and Quality Improvement; **TNF-α,** tumor necrosis factor α

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