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# Optimal Scale-Up of HIV Treatment Programs in Resource-Limited Settings Under Supply Uncertainty

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This study is motivated by the challenges faced by clinics in sub-Saharan Africa in allocating scarce and unreliable supply of antiretroviral drugs (ARVs) among a large pool of eligible patients. Existing discussion of ARV allocation is focused on qualitative rules for prioritizing certain socioeconomic and demographic patient segments over others at the national level. However, such prioritization rules are of limited utility in providing quantitative guidance on scaling up of treatment programs at individual clinics. In this study, we take the perspective of a clinic administrator whose objective is to maximize the quality-adjusted survival of the entire patient population in its service area by allocating scarce and unreliable supply of drugs among two activities: initiating treatment for untreated patients and continuing treatment for previously treated patients. The key trade-off underlying this allocation decision is between the marginal health benefit obtained by initiating an untreated patient on treatment and that obtained by avoiding treatment interruption of a treated patient. This trade-off has not been explicitly studied in the clinical literature, which focuses either on the incremental value obtained from initiating treatment (over no treatment) or on the value of providing continuous treatment (over interrupted treatment) but not on the difference of the two. We cast the clinic's problem as a stochastic dynamic program and provide a partial characterization of the optimal policy, which consists of dynamic prioritization of patient segments and is characterized by state-dependent thresholds. We use this structure of the optimal policy to design a simpler *Two-Period* heuristic and show that it substantially outperforms the *Safety-Stock* heuristic, which is commonly used in practice. In our numerical experiments based on realistic parameter values, the performance of the *Two-Period* heuristic is within 4% of the optimal policy whereas that of the *Safety-Stock* heuristic can be as much as 20% lower than that of the optimal policy. Our model can serve as a basis for developing a decision support tool for clinics to design their ARV treatment program scale-up plans.

*Key words:* inventory rationing; supply uncertainty; global HIV pandemic; antiretroviral treatment
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## 1. Introduction

Many organizations strive to attain a balance between expanding their services to new customers and maintaining quality of service for existing customers. Such trade-off can arise in a wide variety of sectors ranging from non-profit organizations that depend exclusively on donations as well as startups in the initial phase of their lifecycle. This trade-off becomes particularly acute when the organization faces uncertainty in the availability of a key resource. In this article, we study this trade-off in a specific operational context that of scaling up HIV treatment programs in sub-Saharan Africa. HIV clinics in this context receive extremely limited and uncertain supply of antiretroviral drugs (ARVs) that needs to be used for initiating untreated patients on treatment and for continuing treatment for patients who have been previously treated. On one hand, clinics can focus on ensuring continuous treatment to their previously treated patients (Schouten et al. 2011) by being conservative in their scale-up and capping the number of new enrolments. However, this can lead to delay in treatment initiation for untreated patients, which in turn can lead to significant reduction in their quality of life (QOL) and even death due to disease progression (Doherty et al. 2005, Farnham et al. 2013, Ford et al. 2010). On the other hand, clinics can be aggressive by enrolling many new patients but increase the risk of their treatment interruption in future periods

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due to drug stockouts (IRINNews.org 2013a,b, VoA-News.com 2013b), which in turn can lead to adverse clinical outcomes such as treatment failure (Bartlett 2006, Hamers et al. 2012), drug resistance (Pray et al. 2004, WHO 2016), and increased mortality (El-Sadr et al. 2006), and which can necessitate transitioning patients to a much more expensive second line of therapy (Oyugi et al. 2007, Van Oosterhout et al. 2005).

We model this trade-off embedded in the scale-up of ARV treatment programs using a stochastic dynamic programming framework. We classify HIV patients from a clinic's catchment area into the following categories: (i) patients who are not yet clinically eligible to be initiated on treatment based on national guidelines (*ineligible*), (ii) patients who are clinically eligible but have not yet been initiated on treatment (*eligible and untreated*), (iii) patients who have been initiated on treatment earlier and are still responsive to it (*eligible and treated*), and (iv) patients who had been previously initiated on treatment but are now resistant to it due to previous treatment interruptions (*resistant*). Each period, based on the inventory of ARVs and the number of patients in each of the above four categories, the clinic decides the number of *treated* patients and *untreated* patients to treat and sets aside any remaining inventory to be carried over to the next period. Then the following transitions occur:

- New infections are added to the category of *ineligible* patients.
- A fraction of *ineligible* patients move to the category of eligible patients due to natural progression of their disease.
- Some of the *untreated* patients move to the category of *treated* patients upon enrollment.
- A fraction of *treated* patients whose treatment is interrupted in this period move to the category of resistant patients.

Following these transitions, a fraction of patients in each category die and the surviving patients obtain a reward, which is equal to the per-period QOL utility associated with their category. At the end of the period, the clinic receives a shipment of ARVs of an uncertain quantity. The objective of the clinic is to maximize the total expected quality-adjusted life years (QALYs) of its patients over the planning horizon subject to availability of drugs and the number of patients in different segments.

The resulting decision problem is related to but substantially different from the traditional models of multi-product and/or multi-customer inventory rationing (DeCroix and Arreola-Risa 1998, Evans 1967) due to non-stationarity of rewards and endogenous movement of patients across segments depending on whether they received the product in the current period. Consequently, unlike those papers, static prioritization of one (high value) segment over the other (low value) is not optimal for our problem. In contrast, the optimal policy is state dependent and is characterized by thresholds and switching curves that define regions in the state space such that allocation decisions are different across these regions. However, analytical difficulties preclude complete characterization of the optimal policy for the most general version of the problem and make it an unlikely candidate for implementation. Hence, we focus on few special cases to understand the underlying trade-offs. These include the two-period problem as well as two extreme cases of the general multi-period problem: (i) none of the patients with treatment interruption develop drug resistance and (ii) when all patients with treatment interruption develop drug resistance.

Insights from these special cases indicate that the optimal policy for the general formulation, under some conditions, prescribes denying treatment to *treated* patients (i.e., patients already on treatment) to avoid future treatment interruptions. This structure presents an important dilemma pertaining to the social responsibility of the ARV program and is unlikely to be tenable in practice. Hence, based on the structure of the optimal policy for the three special cases described above, we develop a *Two-Period* heuristic which has a far simpler structure that makes it amenable to implementation. Extensive computational experiments show that the average optimality gap of this heuristic is <4% over a wide range of parameter values. In contrast, a *Safety-Stock* heuristic based on current practice (Schouten et al. 2011, WHO 2016) yields average optimality gaps of around 20%. Beyond better overall performance, the *Two-Period* heuristic is also much more robust to misspecification of the parameter values and is no more difficult to implement than the *Safety-Stock* heuristic.

The remainder of the study is organized as follows. In section 2, we describe the operational challenges of scaling up antiretroviral therapy (ART) programs in resource-constrained settings in greater detail. Section 3 outlines our contribution to various streams of related literature. Section 4 provides the model formulation and section 5 presents a partial characterization of the optimal policy and its properties. Section 6 includes a formal description of the two heuristics which are either used in practice or have practical appeal and a procedure for obtaining the upper bound. Section 7 contains extensive numerical illustrations to compare the performance of these heuristics with the optimal policy. We develop an extension

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of our main model and discuss it in section 8. Finally, section 9 provides concluding remarks.

## 2. Operational Challenges in HIV Drug Supply

Benefits of ART in terms of reduced mortality, morbidity, and hospitalization are well established (Ford et al. 2010, Palella et al. 1998, Walensky et al. 2006). Yet the coverage of ART in sub-Saharan Africa, the epicenter of the epidemic, is still abysmally low due to insufficient funding from international donors after the global financial crisis in 2009 (Leach-Kemon et al. 2012, Serieux et al. 2012). To ensure that limited funds are used most effectively, WHO guidelines stipulate strict eligibility criteria such that only individuals with severe or advanced HIV clinical disease (defined as WHO clinical stage 3 or 4 and individuals with CD4 count $\leq$ 350 cells/mm$^3$) can be initiated on ART (WHO 2016). Many countries further restrict eligibility based on clinical, demographic, and socioeconomic factors (Bennett and Chanfreau 2005, Rosen et al. 2005). However, of the 21.2 million patients considered eligible even by these stringent criteria, only 7.5 million were on treatment in 2013 (UNAIDS 2013).

Beyond insufficient funding, logistical constraints further add to the inefficiency in the ARV supply chain. Distribution systems for ARVs in resource-constrained countries consist of central medical depots, typically located in the national capital, from where the drugs are *pushed* to the sites of health care delivery (Harries et al. 2007, WHO 2003, 2005). Inadequate inventory management skills at the clinics make it very difficult to implement a *pull* system, where clinics place orders for drugs with the central medical depots (WHO 2003). Thus, due to weak physical infrastructure, poor supply chain management, and lack of adequate information and transport systems in the supply chain (Bateman 2013, de Vries et al. 2020, Georgeu et al. 2012, Pray et al. 2004, Schouten et al. 2011), the supply actually received at an HIV clinic is highly variable. This aggregate shortage and variability of supply, when combined with sub-optimal allocation policies, leads to periodic stockouts of ARVs (Ekong et al. 2004, IRINNews.org 2013b, VoANews.com 2013a, Wangu and Osuga 2014, Windisch et al. 2011).

A common response to supply uncertainty in practice is to maintain a safety stock of ARVs equivalent to several months of consumption by the *treated* patients and imposing a cap on the number of new patients that can be enrolled in every period (AllAfrica.com 2013, Schouten et al. 2011). Yet the effectiveness of these rules of thumb has not been rigorously studied and there is an acknowledgment among practitioners that more formal models are needed to understand the underlying trade-offs (Daniel 2006).

## 3. Literature Review

The primary contribution of this study is to provide quantitative insights on how HIV clinics in resource-limited settings should scale-up their treatment programs when faced with uncertain and limited drug supply. A secondary contribution, in doing so, is to extend models of multi-item inventory management by incorporating endogenous customer dynamics between different segments and supply uncertainty. We discuss these contributions in the context of three relevant streams of literature related to our study.

### 3.1. HIV Treatment Rationing

Early literature on rationing of ARVs (Bennett and Chanfreau 2005, Macklin 2004, McGough et al. 2005, Rosen et al. 2005, Sharif and Noroozi 2010) is dominated by discussion of prioritization schemes based on socioeconomic and demographic variables (i.e., "which" new patients to enroll) so as to meet ethical criteria such as equity and fairness. Rosen et al. (2005) extends these to include clinical effectiveness, implementation feasibility, cost, economic efficiency, social equity, and provides a qualitative evaluation of various national policies.

However, this discussion has limited utility in making operational decisions on how to scale-up treatment programs at the level of individual clinics because of a lack of quantitative framework. Moreover, it adopts a static perspective, that is, the rationing or prioritization decision is treated as a one-time decision and focuses only on the aggregate shortage of drugs but ignores the uncertainty in the supply of ARVs received at the health facilities.

We address these limitations in a quantitative model which captures the trade-off between initiating new patients on treatment and ensuring treatment continuation of patients already on treatment. This trade-off has not been explored in the clinical literature, which either shows that initiating treatment is better than no treatment through cost-effectiveness studies (Badri et al. 2006, Cleary et al. 2006, Palella et al. 1998) or that continuous treatment is better than interrupted treatment through studies on structured treatment interruptions and impact of treatment adherence (Danel et al. 2006, Lawrence et al. 2003, Paterson et al. 2000).

### 3.2. Global Health Supply Chains

Recent work on global health supply chains represents an important part of the emerging literature on socially responsible operations. Kraiselburd and Yadav (2013) highlight the lack of coordination across multiple donors and the recent reduction in budgetary allocations toward humanitarian aid after the financial crisis as the major challenges at the macro

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level for these supply chains. Taylor and Xiao (2014) compare the effectiveness of purchase vs. sales subsidy in private distribution channels to improve the availability of products from the perspective of donors. Gallien et al. (2017) build a quantitative model to predict the joint impact of procurement and funding delays in global health programs on drug availability and stockouts at the country level. Natarajan and Swaminathan (2014) focus on managing inventory levels of a nutritional product and determining optimal procurement policy by taking into account the uncertainty associated with funding amount and schedule.

We focus on the tactical decisions with the clinic as the decision-making unit and study the impact of operational decisions directly on health outcomes. Similar to our approach, McCoy and Johnson (2014) also consider a multi-period problem faced by a clinic in deciding the number of new patients to enroll in each period so as to minimize the number of infected patients over the problem horizon. However, the main trade-off in their model is between reduced disease transmission due to initiation of new patients on treatment and reduced treatment adherence due to every subsequently enrolled patient living farther from the clinic. They do not consider supply uncertainty and treatment interruption induced by stockouts; the main driver of treatment interruption and drug resistance in their model is reduced adherence of patients to follow-up visits if they live farther from the clinic. Another recent paper that is related to ours is Natarajan and Swaminathan (2017), which analyzes the problem of allocating limited inventory of drugs among patients with different health states. The main point of distinction here is that we model a chronic disease where the patients who receive treatment continue to return in subsequent periods and thus compete for drugs along with new patients whereas Natarajan and Swaminathan (2017) model an acute condition where the patients in the less severe health state are cured after treatment and exit the system. This leads to significant differences in the state transition equations and consequently the structure of the optimal policy. A secondary point of distinction is that Natarajan and Swaminathan (2017) focus on the impact of the timing and the variability in donor funding that is used to procure the drugs whereas our focus is on designing clinic-level program scale-up policies in the presence of an uncertain exogenous supply of drugs.

### 3.3. Inventory Management

Our model is related to the broader literature on periodic review multi-item inventory models with resource constraint (DeCroix and Arreola-Risa 1998, Evans 1967). These models typically include an exogenous and deterministic constraint on the procurement budget in each period and the underage and overage costs of multiple products are also exogenously specified and stationary, which allows ranking them in the order of importance. For continuous time formulations, see Ha (1997) and de Véricourt et al. (2003).

Our model differs from these in two key aspects. On the demand side, the customer segments are inherently related as customers from one pool (*untreated*) are moved permanently to another pool (*treated*) as a result of the treatment decisions. Such dynamics in the product space, corresponding to cross-product substitution, have not been studied previously. Combined with non-stationary cost of not serving each of the two segments, these dynamics yield an interesting result. In some cases, the high-value patient segment is not fully served despite the availability of adequate inventory. This can be interpreted as inter-temporal rationing between patients of the same segment, a feature that is absent from the existing models. In a recent paper, Deng et al. (2014) also consider an inventory model where the demand in future periods depends, among other things, on past service experience of customers. However, in their models, customers from the two segments cannot be distinguished from each other and the focus is on deciding the optimal inventory levels in each period and not the allocation of available inventory among the two segments. On the supply side, the key point of departure from the literature is the uncertainty in the supply and the absence of an ordering decision for the clinics.

## 4. Model Preliminaries

In this section, we present a formal model for the decision problem faced by a resource constrained individual clinic. To reflect the finite planning horizon of such clinics, we consider $N$ discrete periods, where $n = 1$ denotes the last period and $n = N$ denotes the first period. The clinic receives an exogenous uncertain supply of first-line ARVs every period and needs to decide how to allocate the available supply of drugs between *untreated* and *treated* patients so as to maximize the expected quality-adjusted survival of its patients. We first describe various building blocks of our model, and then combine them to formulate the clinic's dynamic decision problem.

### 4.1. Patient Dynamics

We divide the patient population in each period into four broad segments depending on their health status, subsequent clinical eligibility for treatment initiation and sensitivity to first-line ARVs.

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Let $y_{n,i}$ be the number of patients who are *ineligible* for treatment according to the national treatment eligibility guidelines at the beginning of period $n$. Let $y_{n,u}$ denote the number of previously untreated eligible patients, henceforth referred to as *untreated* patients. Similarly, let $y_{n,t}$ denote the number of previously treated patients, who are still responsive to first-line treatment and are henceforth referred to as *treated* patients. Finally, let $y_{n,r}$ be the number of previously treated patients who have failed the first-line of therapy and are henceforth referred to as *resistant* patients.

Next, we describe the transitions between these different segments, which are represented schematically in Figure 1. Note that the demand for first-line ARVs, which is the focus of our analysis, consists of *treated* and *untreated* patients, $y_{n,t}$ and $y_{n,u}$. Let $x_{n,t}$ and $x_{n,u}$ denote the number of *treated* and *untreated* patients that the clinic decides to treat in period $n$.

The pool of *ineligible* patients increases by a factor $\alpha_i$ due to diagnosis of new infections and decreases by a factor $\alpha_e$ due to patients becoming eligible for treatment due to clinical disease progression. A fraction $\beta_i$ of the *ineligible* patients in period $n$ survives to the next period $n-1$. Then, the number of *ineligible* patients at the beginning of period $n-1$ as a result of these transitions is given by:

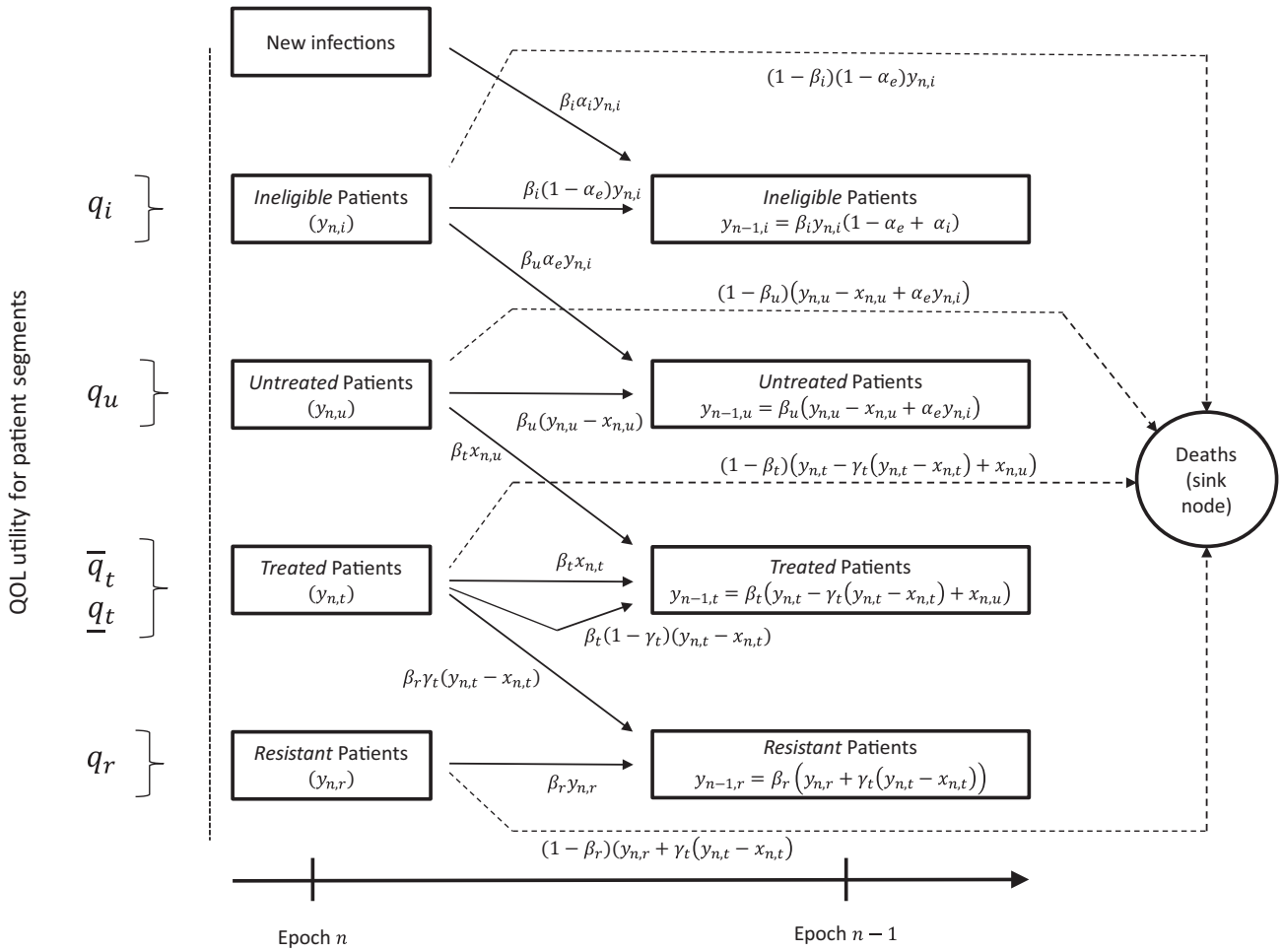
$$y_{n-1,i} = \beta_i\Big(y_{n,i}(1-\alpha_e+\alpha_i)\Big). \tag{1}$$

The pool of *untreated* patients increases by $\alpha_e y_{n,i}$ as *ineligible* patients become eligible due to disease progression and reduces by $x_{n,u}$ due to initiation of patients on treatment. A fraction $\beta_u$ of the *untreated* patients survives to the next period. Thus, the number of eligible *untreated* patients at the beginning of period $n-1$ is given by:

$$y_{n-1,u} = \beta_u\Big(y_{n,u} - x_{n,u} + \alpha_e y_{n,i}\Big) \tag{2}$$

At the beginning of period $n$, the clinic decides to treat $x_{n,t}$ of the $y_{n,t}$ previously treated patients and

**Figure 1 Flow of HIV Patients Through Various Stages of Disease Progression and Treatment**

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enroll $x_{n,u}$ new patients. Of the remaining $(y_{n,t} - x_{n,t})$ patients, who were treated previously but remain untreated in this period, a fraction $\gamma_t$ develop resistance to first-line treatment, which we refer to as the coefficient of resistance. Let $\bar{y}_{n-1,t}$ denote the number of previously treated patients who receive treatment and $\underline{y}_{n-1,t}$ denote the number of patients who do not receive the treatment in period $n$ but are still sensitive to treatment. Then, the number of *treated* patients at the beginning of period $n-1$ is given by:

$$\begin{aligned} y_{n-1,t} &= \bar{y}_{n-1,t} + \underline{y}_{n-1,t} \\ &= \beta_t(x_{n,t} + x_{n,u}) + \beta_t(1-\gamma_t)(y_{n,t} - x_{n,t}) \\ &= \beta_t(y_{n,t} - \gamma_t(y_{n,t} - x_{n,t}) + x_{n,u}) \end{aligned} \tag{3}$$

where $\beta_t$ denotes the survival rate of *treated* patients. We assume that $\beta_t > \beta_u$ as treatment initiation is expected to improve the survival rate of patients.

On the flip side, the pool of resistant patients increases by $\gamma_t(y_{n,t} - x_{n,t})$ due to treatment interruption of some of the *treated* patients. Thus, the number of resistant patients at the beginning of period $n-1$ is given by:

$$y_{n-1,r} = \beta_r(y_{n,r} + \gamma_t(y_{n,t} - x_{n,t})), \tag{4}$$

where the survival rate of resistant patients is given by $\beta_r$. Again, we assume that $\beta_r < \beta_t$ because resistance to first-line treatment is expected to reduce the survival rate of patients. Thus, the system of Equations (1)–(4) represent the patient dynamics in the clinic's decision problem.

REMARK 1. Note that treatment has beneficial impact in terms of reduced transmission, which occurs due to reduced viral load in treated patients. However, this effect is likely to be low under our assumption of constrained resources. Even if we were to modify the dynamics of the *ineligible* patient segment—by introducing an additional term that captures a linear impact of the *treated* patient pool—Proposition 1 continues to hold with minor changes in the coefficients of the decision variables and the states ($\Delta_{n,t}$, $\Delta_{n,u}$, and $\tilde{\Delta}_{n,t}$). Consequently, the dynamic programming formulation and the structure of the optimal policy will not be affected by this change. ∎

### 4.2. Inventory Dynamics

Let $w_n$ denote the opening stock of drugs at the beginning of period $n$, where one unit of drug corresponds to one period of treatment for one patient. Of these, the clinic uses $x_{n,u}$ doses to initiate *untreated* patients on treatment and $x_{n,t}$ doses to treat *treated* patients. To reflect the practical reality that clinics often do not have control over how many doses they receive, we use $z_{n-1}$ to denote the exogenous random supply that the clinic receives at the end of period $n$. Thus, the amount of inventory at the beginning of period $n-1$ is given by:

$$w_{n-1} = w_n - x_{n,t} - x_{n,u} + z_{n-1} = I_{n-1} + z_{n-1}, \tag{5}$$

where $I_n$ denotes the inventory of drugs after the allocation but before the receipt of supply in period $n$. We assume that $z_n$ are independent, but not necessarily identical, random variables with cumulative distribution $F_n(\cdot)$ and support on $[0,\ z_n^U]$. Note that this assumption in our theoretical analysis is meant only to demonstrate the generalizability of our results. Throughout the numerical analysis, we analyze the setting where the supply distribution across all periods is the same and the clinic makes its decisions knowing this information. Given the sufficiently long shelf lives of first-line ARVs, we do not explicitly model the perishability of drugs.

### 4.3. Reward Structure

The objective of the clinic administration is to maximize the total discounted QALYs of the entire patient population (treated and untreated) in the catchment area. It is calculated as the sum of QOL utilities of all patients over the planning horizon, discounted to account for the fact that an additional year of life today is worth more than that in the future (Vergel and Sculpher 2008, Whitehead and Ali 2010). This objective function is routinely used in cost-effectiveness studies (Brennan et al. 2006) and resource allocation problems (Brandeau et al. 2003, Deo et al. 2013, Richter et al. 1999, Zenios et al. 2000).

Let $q_i$ and $q_u$ denote the QOL utility for *ineligible* and *untreated* patients. For the pool of *treated* patients, we assume that the patients who continue to receive treatment in that period (given by $\bar{y}_{n-1,t}$ in period $n$) enjoy a QOL utility of $\bar{q}_t$ while the patients whose treatment has been interrupted in that period but are still sensitive to treatment (given by $\underline{y}_{n-1,t}$ in period $n$) get a QOL utility of $\underline{q}_t < \bar{q}_t$. Furthermore, the patients who do not receive treatment and develop resistance to first-line treatment move to the pool of resistant patients and receive a QOL utility of $q_r$. QOL utilities associated with each of the patient segments are indicated on the left-hand side of Figure 1.

Then the reward collected by the clinic at the end of period $n$ is given by:

$$\begin{aligned} h_n(\mathbf{y}_{n-1}) = \ & \bar{q}_t \bar{y}_{n-1,t} + \underline{q}_t \underline{y}_{n-1,t} \\ & + q_u y_{n-1,u} + q_r y_{n-1,r} + q_i y_{n-1,i} \end{aligned}$$

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where $\mathbf{y}_{n-1} \triangleq [\bar{y}_{n-1,\ t}\underline{y}_{n-1,\ t}y_{n-1,\ u}y_{n-1,\ r}y_{n-1,i}]^t$. Substituting the expressions for each of the variables in terms of the state variables and decisions from (1) to (4) and similarly defining $\mathbf{x}_n \triangleq [x_{n,t}x_{n,u}]^t$, we obtain:

$$h_n(\mathbf{x}_n, \mathbf{y}_n) = (\bar{q}_t\beta_t - q_u\beta_u)x_{n,u} + \left((\bar{q}_t - \underline{q}_t(1-\gamma_t))\beta_t - \gamma_t q_r\beta_r\right)x_{n,t} + y_{n,u}(q_u\beta_u) + y_{n,r}(q_r\beta_r) + y_{n,t}\left(\underline{q}_t(1-\gamma_t)\beta_t + q_r\gamma_t\beta_r\right) + y_{n,i}(q_i\beta_i(1-\alpha_e+\alpha_i) + q_u\alpha_e\beta_u) \quad (6)$$

### 4.4. Model Formulation

Using the above components, now we can state the decision problem of the clinic as follows:

$$\max_{x_{n,t}\geq 0,\ x_{n,u}\geq 0} \mathbb{E}\left[\sum_{n=1}^{N}\delta^{N-n}h_n(\mathbf{x}_n, \mathbf{y}_n)\right] \quad (7)$$
s.t. (1), (2), (3), (4), (5)

$$x_{n,t} + x_{n,u} \leq w_n \forall n, \quad (8)$$

$$x_{n,t} \leq y_{n,t} \forall n, \quad (9)$$

$$x_{n,u} \leq y_{n,u} \forall n. \quad (10)$$

Equations (1)–(5) are the patient and inventory dynamics described earlier. Constraint (8) states that the total number of treatments delivered in period $n$ is limited by the available inventory. Constraints (9) and (10) state that the number of *treated* and *untreated* patients treated cannot be more than the total number of *treated* and *untreated* patients in that period, respectively.

Next, we note from the above formulation that the decisions $\mathbf{x}_n$ do not depend on $y_{n,i}$ and $y_{n,r}$. Hence, we use the recursive in Equations (1) and (4) to derive expressions for these state variables in terms of the initial conditions in period $N$ and subsequent treatment decisions. Furthermore, to reflect the extreme resource-constrained nature of our application setting, we assume that number of *untreated* patients outstrips the available supply of drugs throughout the problem horizon for all feasible allocation policies, that is, $y_{n,u} > w_n \forall n$. This allows us to reformulate an equivalent dynamic program with reduced state space, which is formalized in Proposition 1(ii) below.

PROPOSITION 1 (Problem reformulation).

(i) *The equations for state variables $y_{n,r}$, $y_{n,i}$ and $y_{n,u}$ $\forall$ $n$ are as follows:*

$$y_{n,r} = y_{N,r}\beta_r^{N-n} + \gamma_t\sum_{j=1}^{N-n}\left(y_{n+j,t} - x_{n+j,t}\right)(\beta_r)^j \quad (11)$$

$$y_{n,i} = y_{N,i}(\beta_i(1-\alpha_e+\alpha_i))^{N-n} \quad (12)$$

$$y_{n,u} = \beta_u^{N-n}y_{N,u} - \sum_{j=1}^{N-n}\beta_u^j x_{n+j,u} + \beta_i\alpha_e\sum_{j=1}^{N-n}\beta_u^{j-1}y_{n+j,i} \quad (13)$$

(ii) *If $y_{n,u} > w_n \forall n$, then the decision problem as stated in (7) can be equivalently reformulated as:*

$$V_n\left(y_{n,t}, w_n\right) = \max_{x_{n,t}\geq 0,\ x_{n,u}\geq 0}\left\{\hat{h}_n\left(\mathbf{x}_n, y_{n,t}\right) + \delta\mathbb{E}_z\left[V_{n-1}\left(y_{n-1,t}, w_{n-1}\right)\right]\right\} \quad (14)$$
s.t. (3), (5)

$$x_{n,t} + x_{n,u} \leq w_n$$

$$x_{n,t} \leq y_{n,t}$$

$$\text{and } V_0(y_{0,t}, w_0) = 0$$

$$\text{where } \hat{h}_n(\mathbf{x}_n, y_{n,t}) = \Delta_{n,t}x_{n,t} + \Delta_{n,u}x_{n,u} + \tilde{\Delta}_{n,t}y_{n,t} \quad (15)$$

$$\Delta_{1,u} = \left(\bar{q}_t\beta_t - q_u\beta_u\right) \quad (16)$$

$$\Delta_{1,t} = (\bar{q}_t - \underline{q}_t(1-\gamma_t))\beta_t - \gamma_t q_r\beta_r \quad (17)$$

$$\Delta_{n,u} = \begin{cases} \Delta_{1,u} - q_u\beta_u\sum_{j=1}^{n-1}(\delta\beta_u)^j & n \geq 2 \\ \left(\bar{q}_t\beta_t - q_u\beta_u\right) & n = 1 \end{cases} \quad (18)$$

$$\Delta_{n,t} = \begin{cases} \Delta_{1,t} - \gamma_t q_r\beta_r\sum_{j=1}^{n-1}(\delta\beta_r)^j & n \geq 2 \\ (\bar{q}_t - \underline{q}_t(1-\gamma_t))\beta_t - \gamma_t q_r\beta_r & n = 1 \end{cases} \quad (19)$$

$$\tilde{\Delta}_{n,t} = \bar{q}_t\beta_t - \Delta_{n,t} \quad n \geq 1 \quad (20)$$

*In other words, under the assumption of extreme resource constraint $y_{n,u} > w_n$, any optimal solution to (7) is an optimal solution to (14) and vice versa.*

Note that the immediate marginal social benefits of treating a patient from the two segments in period $n$,

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$\Delta_{n,t}$ and $\Delta_{n,u}$, are non-stationary and are functions of the patient transition parameters because of our focus on population-level outcomes in the presence of constrained resources. In contrast, the focus of most of the clinical literature has been on comparing individual marginal benefits of treating *treated* and *untreated* patients ($\Delta_{1,t}$ and $\Delta_{1,u}$) by implicitly ignoring the resource constraint and the effect of current treatment decisions on the pool of patients in the future periods (e.g., Granich et al. 2009).

Furthermore, the single period marginal benefits of treating a patient from the two segments do not have a clear and stable ranking over the problem horizon, unlike existing models of multi-product inventory management under budget constraint (DeCroix and Arreola-Risa 1998, Evans 1967) where these rewards are essentially the single period shortage costs for the two segments. In other words, in our context, a segment that is more important in the current period could become less important in a future period and vice versa–a feature that is absent from those existing models. Since the main underlying driver for this effect is the coefficient of resistance $\gamma_t$ as seen from (19) and (20), we solve special instances of the formulation (14) corresponding to extreme values of $\gamma_t$ to obtain further insights.

# 5. Partial Characterization of the Optimal Policy

A complete characterization of the dynamic program (14) would require distinguishing between many cases corresponding to different relative rankings of the QOL utility parameters ($\bar{q}_t$, $\underline{q}_t$, $q_u$, $q_r$). To make the analysis more manageable, we restrict our attention to QOL utilities that are consistent with the clinical definitions of various patient segments and that yield nontrivial inventory allocation decisions. We begin by assuming that the *treated* patients who received the treatment in a given period earn the highest QOL utility among all patient segments who are eligible for HIV treatment ($\bar{q}_t > \underline{q}_t$, $q_u$, $q_r$). Furthermore, we assume that $\underline{q}_t > q_r$, that is, the patients who do not receive the treatment but are sensitive to first-line therapy enjoy a better QOL utility than the patients who have developed resistance to treatment. Finally, some cases are trivial: When $q_u < \underline{q}_t$, $q_r$ that is, when *untreated* patients enjoy a lower QOL utility than *treated* patients who do not receive treatment and resistant patients, it is optimal to prioritize *treated* patients in all periods and exhaust the available inventory of drugs, that is, $x^*_{n,u} = w_n$ and $x^*_{n,t} = 0$ because $y_n > w_n \, \forall \, n$. Hence, to focus on nontrivial and interesting cases, we assume that $\bar{q}_t > \underline{q}_t$, $q_u > q_r$ throughout our analysis.

## 5.1. Two-Period Problem

In this section, we analyze a two-period problem, which is the smallest nontrivial problem instance that captures the trade-off between initiating *untreated* patients on treatment now vs. reducing the chance of treatment interruption for *treated* patients later. The structure of the optimal policy depends on the relative values of the QOL utilities of various patient segments and the coefficient of resistance, which is formally stated in Proposition 1. In section 6.2, we use this structure to develop a heuristic for the more general multi-period problem that is computationally tractable and performs well.

PROPOSITION 2. *There exist* $0 \le \gamma_1, \ \gamma_2 \le 1$ (*defined in the Appendix such that for period* $n = 2$),

(i) *If* $\underline{q}_t > q_u$ *and* $0 \le \gamma_t < \min\{\gamma_1, \gamma_2\}$, *the optimal policy is to prioritize untreated patients over treated patients and exhaust the available inventory of drugs, that is,* $x^*_{2,u} = w_2$ *and* $x^*_{2,t} = 0$.

(ii) *If* $\underline{q}_t > q_u$ *and* $0 < \gamma_2 < \gamma_t \le \gamma_1$, *the optimal policy is to prioritize treated patients over untreated patients and exhaust the available inventory of drugs, that is,* $x^*_{2,u} = [w_2 - y_{2,t}]^+$ *and* $x^*_{2,t} = \min\{y_{2,t}, w_2\}$.

(iii) *If* $\underline{q}_t > q_u$ *and* $\gamma_1 < \gamma_t \le 1$ *or if* $\underline{q}_t < q_u$ *and* $0 \le \gamma_t \le 1$ *the optimal policy is to prioritize treated patients over untreated patients and to keep some drugs in inventory* (*see Table* 1 *and Figure* 2).

**Table 1 Two-Period Optimal Policy Structure for Conditions State in Proposition 2(iii)**

| | | Optimal policy | | |
|---|---|---|---|---|
| **Region** | **State space** | $x^*_{2,u}$ | $x^*_{2,t}$ | $w_2 - x^*_{2,u} - x^*_{2,t}$ |
| $TP_A$ | $0 \le y_{2,t} \le w_2 < \frac{\theta_{2,u}}{\beta_t}$ | $w_2 - y_{2,t}$ | $y_{2,t}$ | 0 |
| $TP_B$ | $0 \le y_{2,t} \le w_2 \cap w_2 \ge \max\{\frac{\theta_{2,u}}{\beta_t}, \, y_{2,t}(1+\beta_t) - \theta_{2,u}\}$ | $\frac{w_2 + \theta_{2,u}}{1+\beta_t} - y_{2,t}$ | $y_{2,t}$ | $\frac{w_2\beta_t - \theta_{2,u}}{1+\beta_t}$ |
| $TP_C$ | $y_{2,t} \ge \frac{\theta_{2,u}}{\beta_t} \cap y_{2,t} \le w_2 \le y_{2,t}(1+\beta_t) - \theta_{2,u}$ | 0 | $y_{2,t}$ | $w_2 - y_{2,t}$ |
| $TP_D$ | $0 \le w_2 \le y_{2,t}$ | 0 | $w_2$ | 0 |

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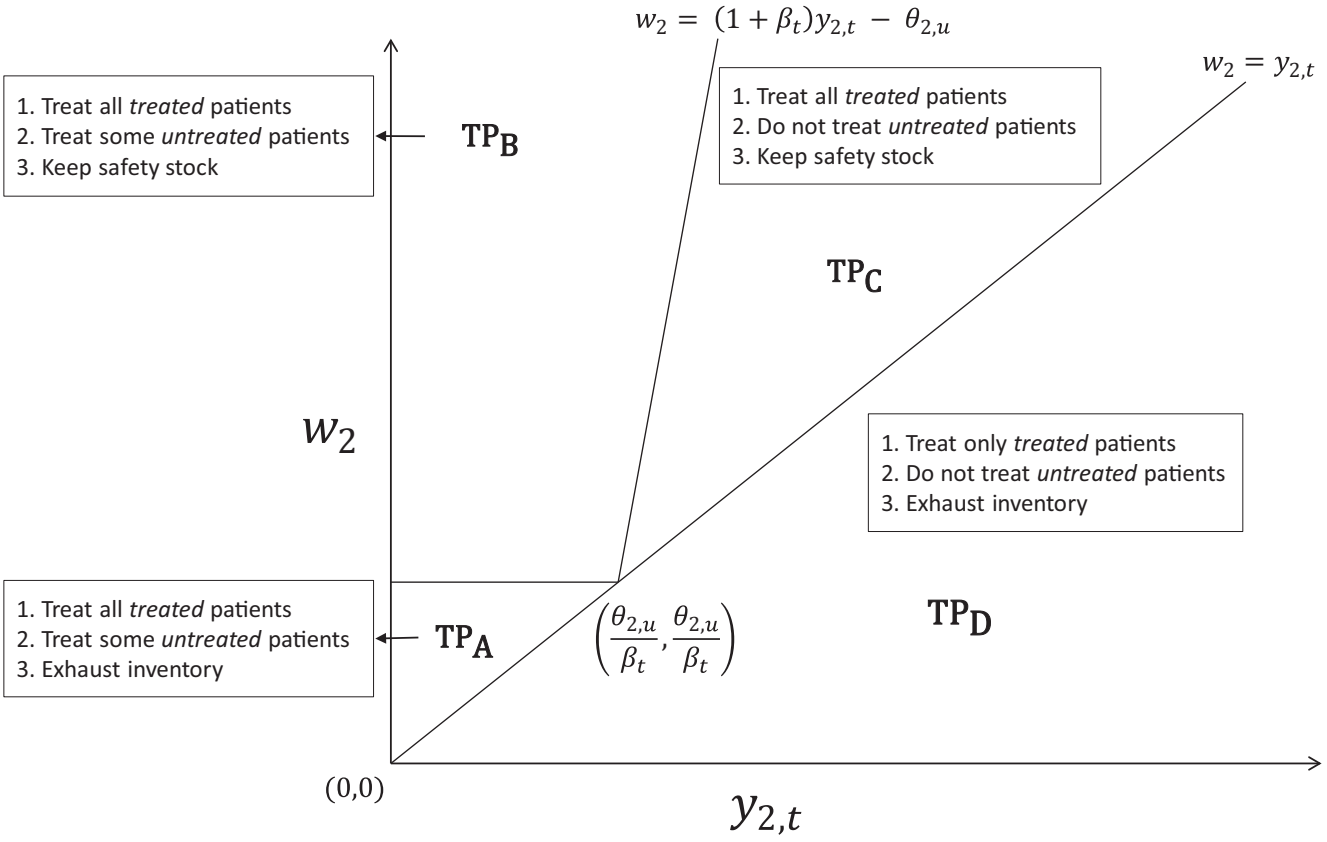
**Figure 2 Characterization of Two-Period Optimal Policy for Conditions Stated in Proposition 2(iii)**




Begin by considering the case when $\underline{q}_t > q_u$, that is, a *treated* patient with interrupted treatment has higher QOL utility than an *untreated* patient. Intuitively, one would think that it must be optimal to prioritize *untreated* patients over *treated* patients under this scenario because the immediate marginal benefit obtained from treating an *untreated* patient is greater than that obtained from treating a *treated* patient who stopped receiving treatment, that is, $\bar{q}_t - \underline{q}_t < \bar{q}_t - q_u$. However, this comparison does not account for the likelihood of developing resistance upon treatment interruption and the QOL for resistant patients $q_r$. Proposition 1 shows that, after accounting for these effects, prioritizing *untreated* patients is optimal only when the coefficient of resistance is sufficiently low, that is, when $0 \le \gamma_t < \min\{\gamma_1, \gamma_2\}$ but the prioritization reverses when it is sufficiently large ($\gamma_t > \gamma_1$ or $0 < \gamma_2 < \gamma_t \le \gamma_1$).

Since the pool of *untreated* patients is infinitely large, prioritizing that segment (Proposition 2(i)) results in all inventory being utilized. Similarly, when prioritizing *treated* patients, it is optimal to exhaust all the inventory when coefficient of resistance is sufficiently low (Proposition 2(ii)). However, for sufficiently high values of the coefficient of resistance ($\gamma_t > \gamma_1$), Table 1 and Figure 2 show that whether it is optimal to utilize all available inventory depends on the relative magnitudes of available inventory and *treated* patient pool.

Specifically, for any given value of the *treated* patient pool, it is optimal to carry a safety stock by restricting the enrollment of *untreated* patients, if the available inventory is greater than a certain threshold (Region $TP_B$). In this region, the optimal safety stock level is $\frac{w_2\beta_t - \theta_{2,u}}{1+\beta_t}$ so as to protect against future treatment interruptions. However, when the *treated* patient pool is sufficiently large (Region $TP_C$), there might not be enough inventory available to hold this level of safety stock. In such cases, it is optimal to not initiate any *untreated* patient on treatment even though there is inventory on hand as drug stockouts in future periods may lead to patients developing resistance.

Finally, when $\underline{q}_t < q_u$, treating a *untreated* patient yields a lower marginal benefit than treating a *treated* patient, irrespective of the value of the coefficient of resistance ($\gamma_t$). In such cases, the optimal policy coincides with that for $\underline{q}_t > q_u$ and high coefficient of resistance (Table 1, Figure 2).

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### 5.2. *N*-Period Problem: Special Cases

Next, we turn our attention to the more general problem of $N > 2$ periods. Characterizing the optimal policy for this general problem is analytically challenging. Specifically, the structure of the optimal policy seems to depend critically on the coefficient of resistance. Consequently, we focus on instances of the problem at extreme values of the coefficient of resistance, that is $\gamma_t = 0$ and $\gamma_t = 1$, for several reasons. First, these cases are analytically tractable. Moreover, as we show later, the insights from the structure of the optimal policy for these special cases allow us to construct a heuristic that performs well for more realistic problems ($0 < \gamma_t < 1$).

PROPOSITION 3. *Assume treatment interruption never leads to drug resistance, that is, $\gamma_t = 0$. Then:*

(i) *If $\underline{q}_t \geq q_u$, then it is optimal to prioritize untreated patients over treated patients in all periods and exhaust the available inventory of drugs that is $x^*_{n,u} = w_n$ and $x^*_{n,t} = 0$.*
(ii) *If $q_u > \underline{q}_t$, then it is optimal to prioritize treated patients over untreated patients and the optimal policy is given by Table 2, where $\phi^{-1}_{n,u}(y_{n,t})$ is a monotonically increasing function such that $\phi^{-1}_{n,u}(\theta_{n,u}) = \theta_{n,u}$.*

Proposition 3 characterizes the optimal policy for the case $\gamma_t = 0$. When $\underline{q}_t \geq q_u$, the benefit from initiating all the patients in the *untreated* pool on treatment exceeds that from allocating the drugs to the patients already on treatment in the *treated* pool, since, even upon treatment interruption, the patients enjoy a higher QOL than not being initiated on the treatment. On the other hand, when $q_u > \underline{q}_t$, the patients in the *untreated* pool may be worse off upon treatment initiation in the event of supply shortage in the future periods; Table 2 states the optimal policy in this case and Figure 3 gives a pictorial illustration of the policy.

It is clear that the structure of the optimal policy for the case $\gamma_t = 0$ with $q_u > \underline{q}_t$ is consistent with that for the two-period problem discussed above with a few differences as highlighted in Figure 3. First, note that the linear function $w_2 = (1 + \beta_t)y_{2,t} - \theta_{2,u}$ that separates region $TP_B$ and $TP_C$ (in Figure 2) is replaced by a nonlinear monotone function $\phi^{-1}_{n,u}(y_{n,t})$ in period $n$ that separates the regions $Z_B$ and $Z_C$ (in Figure 3). Second, in region $Z_B$—characterized by intermediate values of $y_{n,t}$ and a relatively high value of $w_n$—it is optimal to maintain a safety stock of drugs which helps restrict enrollment of *untreated* patients to avoid treatment interruption in subsequent period. This result stems from the fact that even though treatment interruption does not lead to resistance (since $\gamma_t = 0$), the patients whose treatment have been interrupted enjoy a lower QOL than *untreated* patients (as $q_u > \underline{q}_t$) for the rest of the horizon. Furthermore, in this region, $x^*_{n,t} + x^*_{n,u} = \phi_{n,u}(w_n)$. Thus, the term $\phi_{n,u}(w_n)$ can be interpreted as the optimal *treat up-to level*, that is, the total number of treatments to be disbursed in period $n$ for both *untreated* and *treated* patients. Consequently, $(w_n - \phi_{n,u}(w_n))$ represents the optimal amount of safety stock to be carried over to the next period. Finally, when the supply is insufficient to treat all *treated* patients and reach this level of safety stock (Regions $Z_C$ and $Z_D$), then it is optimal to not treat any *untreated* patient.

We now discuss the case when treatment interruption always leads to drug resistance, that is, $\gamma_t = 1$.

PROPOSITION 4. *If $\gamma_t = 1$, then the optimal policy is given by Table 3, where $\phi_{n,t}(\cdot)$ and $\phi_{n,u}(\cdot)$ are monotonically increasing functions and pass through the points $(\theta_{n,t}, \theta_{n,t})$ and $(\theta_{n,u}, \theta_{n,u})$ in the $(y_{n,t}, w_n)$ state space.*

Proposition 4 states the optimal policy for the case $\gamma_t = 1$. From Table 3 and Figure 4, note that the structure of the optimal policy for $\gamma_t = 1$ is very similar to that for $\gamma_t = 0$. In particular, the regions $Z_A$ and $Z_B$ in Figure 3 and the corresponding optimal policy in those regions are exactly the same as the regions $F_A$ and $F_B$ in Figure 4 and the corresponding optimal policy in those regions, respectively. The key point of distinction between the optimal policy for $\gamma_t = 0$ and

**Table 2** ***N*-Period Optimal Policy Structure for $\gamma_t = 0$**

| | | Optimal policy | | |
|---|---|---|---|---|
| **Region** | **State space** | $x^*_{n,u}$ | $x^*_{n,t}$ | $w_n - x^*_{n,t} - x^*_{n,u}$ |
| $Z_A$ | $0 \leq y_{n,t} \leq w_n < \theta_{n,u}$ | $w_n - y_{n,t}$ | $y_{n,t}$ | 0 |
| $Z_B$ | $0 \leq y_{n,t} \leq w_n \cap w_n \geq \max\{\theta_{n,u},\ \phi^{-1}_{n,u}(y_{n,t})\}$ | $\phi_{n,u}(w_n) - y_{n,t}$ | $y_{n,t}$ | $w_n - \phi_{n,u}(w_n)$ |
| $Z_C$ | $y_{n,t} \geq \theta_{n,u} \cap y_{n,t} \leq w_n \leq \phi^{-1}_{n,u}(y_{n,t})$ | 0 | $y_{n,t}$ | $w_n - y_{n,t}$ |
| $Z_D$ | $0 \leq w_n \leq y_{n,t}$ | 0 | $w_n$ | 0 |

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**Figure 3 Characterization of *N*-Period Optimal Policy for $\gamma_t = 0$**

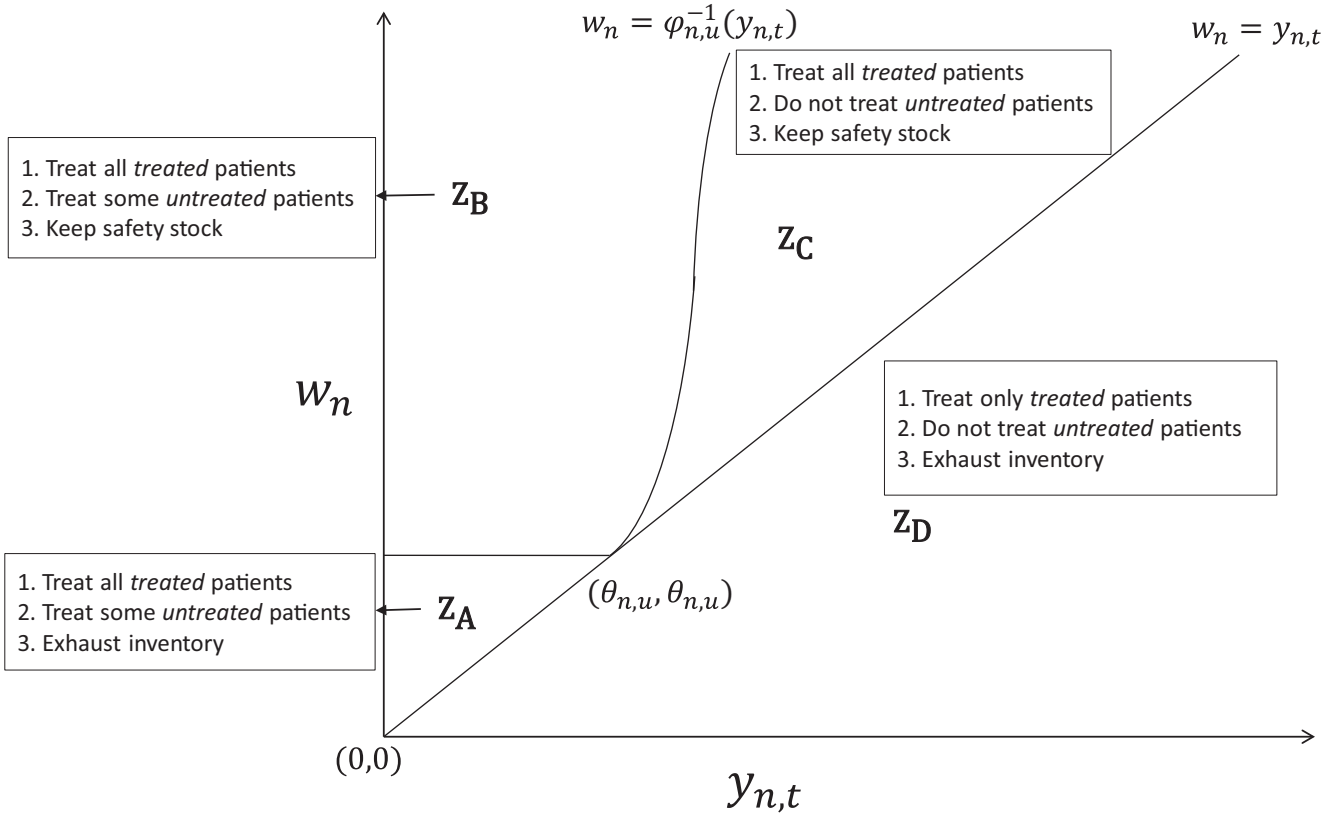


**Table 3 Optimal Policy Structure for $\gamma_t = 1$**

| | | Optimal policy | | |
|---|---|---|---|---|
| **Region** | **State space** | $x_{n,u}^*$ | $x_{n,t}^*$ | $w_2 - x_{n,t}^* - x_{n,u}^*$ |
| $F_A$ | $0 \le y_{n,t} \le w_n < \theta_{n,u}$ | $w_n - y_{n,t}$ | $y_{n,t}$ | 0 |
| $F_B$ | $0 \le y_{n,t} \le w_n \cap w_n \ge \max\{\theta_{n,u}, \phi_{n,u}^{-1}(y_{n,t})\}$ | $\phi_{n,u}(w_n) - y_{n,t}$ | $y_{n,t}$ | $w_n - \phi_{n,u}(w_n)$ |
| $F_C$ | $0 \le y_{n,t} \le w_n \cap \phi_{n,t}^{-1}(y_{n,t}) \le w_n \le \phi_{n,u}^{-1}(y_{n,t})$ | 0 | $y_{n,t}$ | $w_n - y_{n,t}$ |
| $F_D$ | $0 \le w_n \le y_{n,t} \cap w_n < \theta_{n,t}$ | 0 | $w_n$ | 0 |
| $F_E$ | $y_{n,t} \ge \theta_{n,t} \cap \theta_{n,t} \le w_n \le \phi_{n,t}^{-1}(y_{n,t})$ | 0 | $\phi_{n,t}(w_n)$ | $w_n - \phi_{n,t}(w_n)$ |

$\gamma_t = 1$ is that the region $Z_D$ in Figure 3 for $\gamma_t = 0$ is split into two sub-regions $F_D$ and $F_E$ in Figure 4 for $\gamma_t = 1$. Furthermore, the structure of the optimal policy in region $F_D$ is similar to that in region $Z_D$, but that in $F_E$ is significantly different. Table 3 shows that, even though it is optimal to prioritize *treated* patients over *untreated* patients in this region, it is not optimal to utilize all available inventory for *treated* patients but to leave some *treated* patients untreated. This result is different from those in the traditional inventory rationing literature, where it is always optimal to satisfy the entire demand from the high-value segment. The intuition behind this result is that treating all *treated* patients might be beneficial in the current period but increases the pool of *treated* patients and can result in more treatment interruptions and, consequently, more resistant patients, in the event of supply shortage in the subsequent periods. We clarify this intuition using an illustrative sample path in the example below.

EXAMPLE 1. Consider a decision problem over four periods, that is, $N = 4$. Suppose at the beginning of the problem horizon $y_{4,t} = y_{4,u} = 2$ and $I_4 = 0$. Furthermore, assume that $z_1 = z_3 = 2$ and $z_2 = z_4 = 0$. Now consider a "No Buffer" policy wherein, if possible, available drugs are used to satisfy the entire demand from *treated* patients. According to this

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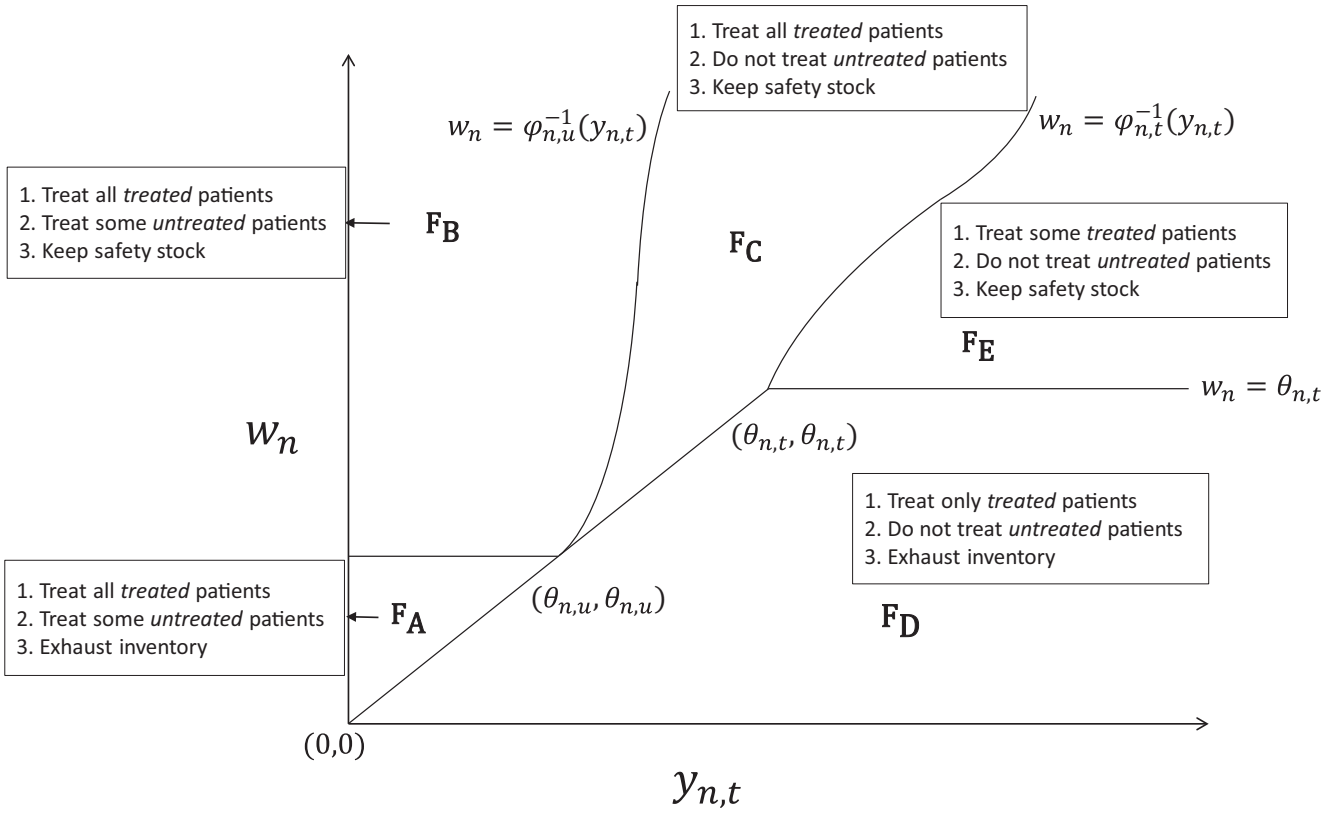
**Figure 4 Characterization of *N*-Period Optimal Policy for $\gamma_t = 1$**




policy, $x_{4,t} = 2$ and $x_{4,u} = 0$ leading to $w_3 = 0$. Consequently, $x_{3,t} = x_{3,u} = 0$ and both *treated* patients will turn resistant from $n = 3$ due to stockout-induced treatment interruption. The next drug supply arrives in $n = 2$ so that $w_2 = 2$, $y_{2,t} = 0$, $y_{2,u} = 2$. Then, clearly $x_{n,u} = 2$, that is, the two *untreated* patients are initiated on treatment but they turn resistant in the last period because of stockout-induced treatment interruption. The QOL utilities earned by the patients is shown in Table 4. Assuming $\delta \approx 1$, the total QALYs for this "No Buffer" policy are $4\bar{q}_t + 8q_r + 4q_u$. Now consider an alternative "Buffer" policy that allocates 1 unit of drug to 1 *treated* patient in all periods and thus keeps a buffer stock of 1 in $n = 4, 2$. As a result, one of the *treated* patients turns resistant from $n = 3$ and the two *untreated* patients never receive any treatment. The total QALYs for the "Buffer" policy are $4\bar{q}_t + 4q_r + 8q_u$. Since $q_u > q_r$, it is clear that the "Buffer" policy outperforms the "No Buffer" policy.

**Table 4 Example to Illustrate that it Need Not be Optimal to Utilize All Drugs When Prioritizing *treated* Patients for $\gamma_t = 1$**

| | "No Buffer" policy | | | | "Buffer" policy | | | |
|---|---|---|---|---|---|---|---|---|
| Period | 4 | 3 | 2 | 1 | 4 | 3 | 2 | 1 |
| Supply $z$ | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 |
| QALY-*treated* patient 1 | $\bar{q}_t$ | $q_r$ | $q_r$ | $q_r$ | $\bar{q}_t$ | $\bar{q}_t$ | $\bar{q}_t$ | $\bar{q}_t$ |
| QALY-*treated* patient 2 | $\bar{q}_t$ | $q_r$ | $q_r$ | $q_r$ | $q_r$ | $q_r$ | $q_r$ | $q_r$ |
| QALY-*untreated* patient 3 | $q_u$ | $q_u$ | $\bar{q}_t$ | $q_r$ | $q_u$ | $q_u$ | $q_u$ | $q_u$ |
| QALY-*untreated* patient 4 | $q_u$ | $q_u$ | $\bar{q}_t$ | $q_r$ | $q_u$ | $q_u$ | $q_u$ | $q_u$ |

It is worth noting that the above policy, which is optimal from the perspective of the overall population QOL, can present an ethical dilemma for the clinic administration if some *treated* patients are to be denied treatment even when inventory of drugs is available. To help address this dilemma in practice, we propose two heuristics in the next section, which impose the constraint that all *treated* patients should be treated in each period as long as sufficient inventory is available in that period. Administrators can then qualitatively trade-off the loss in optimality by following these heuristics with the ethical difficulty of holding back treatment from *treated* patients in the presence of sufficient inventory.

## 6. Heuristics and Upper Bound

As discussed above, analytical difficulties prevent us from characterizing the optimal policy structure for the general multi-period problem for intermediate

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values of the coefficient of resistance ($0 < \gamma_t < 1$). Hence, we develop two heuristic approaches to obtain feasible solutions for the more general problem. The first approach (*Safety-Stock*) is similar to that taken by practitioners in the field and the second (*Two-Period*) is motivated by the structure of the optimal policy derived for the special cases above. Finally, we also construct an upper bound on the optimal objective function in (14) to evaluate the performance of these heuristics. Note that our objective behind numerical analysis of the two heuristics is to distinguish between current practice (*Safety-Stock* heuristic in its current form) and insights from the formal analysis of the underlying trade-offs (*Two-Period* heuristic).

### 6.1. *Safety-Stock* Heuristic

A common approach recommended in practice to manage the scale-up of ART programs is to maintain a safety stock equivalent to few months of demand to buffer against supply uncertainty and consequent treatment interruptions in the future. An equivalent approach is to designate enrollment caps, that is, a maximum number of *untreated* patients that can be enrolled in every period. For instance, Schouten et al. (2011) describe how Malawi's Ministry of Health along with UNICEF has used this approach to scale-up their ART program since 2004. We abstract from the implementation details and formalize the heuristic using our modeling framework as follows.

First, prioritize the treatment of *treated* patients. Obviously, no *untreated* patients can be enrolled if the supply is already exhausted, that is, $x^*_{n,u} = 0$ if $y_{n,t} \geq w_n$. However, if the supply is in excess of the *treated* patients, that is, $y_{n,t} < w_n$, then treat all the *treated* patients first, that is, $x^*_{n,t} = y_{n,t}$ and enroll *untreated* patients such that $y_{n-1,t} = y_{n,t}$. The safety stock carried to the next period is proportional to the number of *treated* patients in the next period. More formally, $I_{n-1} = A y_{n-1,t}$, where the proportionality constant $A$ can be interpreted as the number of months of demand that is carried over as safety stock. From (5), we have $I_{n-1} = w_n - x_{n,t} - x_{n,u}$. Consequently, the number of *untreated* patients to be treated is calculated as $x^*_{n,u} = [w_n - x^*_{n,t} - I_{n-1}]^+$. In summary,

$$x^*_{n,t} = \min\{y_{n,t},\ w_n\},$$
$$x^*_{n,u} = \left(\frac{w_n - x_{n,t}(1 + A\gamma_t) - A y_{n,t}(1 - \gamma_t)}{1 + A}\right)^+.$$

The state space is partitioned into two regions depending on the relative values of $w_n$ and $y_{n,t}$. Clearly, the performance of this heuristic will depend on the value of $A$. Lower values of $A$ correspond to lower safety stock and increased risk of treatment interruptions in the future periods whereas higher values of $A$ correspond to greater safety buffer and fewer *untreated* patients being initiated on treatment in the current period. In our numerical experiments, we perform line search over a sufficiently large interval to compute the best value of $A$ which we denote by $A^*$.

### 6.2. *Two-Period* Heuristic

We develop a heuristic that draws on the insights of the $N$-period optimal policies for extreme values of the coefficient of resistance ($\gamma_t = 0$ and $\gamma_t = 1$) and the two-period optimal policy for intermediate values of the coefficient of resistance. Recall that in those optimal policies, we do not have a closed-form expressions for the parameter $\theta_{n,u}$ for $n > 2$. Furthermore, the expression for the curves $\phi^{-1}_{n,u}(\cdot)$ and $\phi^{-1}_{n,t}(\cdot)$, $n \geq 2$, that separate different regions in the state space are complex. Hence, we make the following simplifications while retaining key elements from the structure of those optimal policies to obtain good performance: First, we replace the parameter $\theta_{n,u}$ with $\theta_{2,u} = F^{-1}\left(1 + \frac{\Delta_{2,u} + \delta(\tilde{\Delta}_{1,t} - \Delta_{1,t})}{2\delta(\Delta_{1,t} - \Delta_{1,u})}\right)$ for all $n$. Second, we replace the curve $w_n = \phi^{-1}_{n,u}(y_{n,t})$ with the linear function $w_n = n y_{n,t} - (n-1)\theta_{2,u}$ for all $n$, based on the following intuition: In the optimal policy for $\gamma_t = 1$, the curve $w_n = \phi^{-1}_{n,u}(y_{n,t})$ separates the region $F_B$ (where some *untreated* patients are initiated on treatment) from $F_C$ (where no patient from the *untreated* pool is initiated on treatment). For a fixed level of inventory, note that as one approaches the end of horizon (i.e., as $n$ decreases) the risk from initiating *untreated* patients on treatment reduces, which in turn implies that the slope of the curve $w_n = \phi^{-1}_{n,u}(y_{n,t})$ decreases. Third, to address the ethical dilemma that arises in region $F_E$ of the optimal policy for $\gamma_t = 1$, we prioritize the treatment of *treated* patients and exhaust the inventory if the patients in the *treated* pool outstrip the supply. This constraint naturally eliminates region $F_E$ and helps simplify the curve $w_n = \phi^{-1}_{n,t}(y_{n,t})$ to $w_n = y_{n,t}$ for all $n$. These three modifications ensure that the structure of the optimal $N$-period policies for $\gamma_t = 0$ and $\gamma_t = 1$ and the optimal two-period policy for intermediate values of $\gamma_t$ is retained to the extent possible and consequently, as we will see below, helps achieve better performance. The resulting structure of the heuristic, which we refer to as *Two-Period* heuristic, is shown in Figure 5. Under this heuristic:

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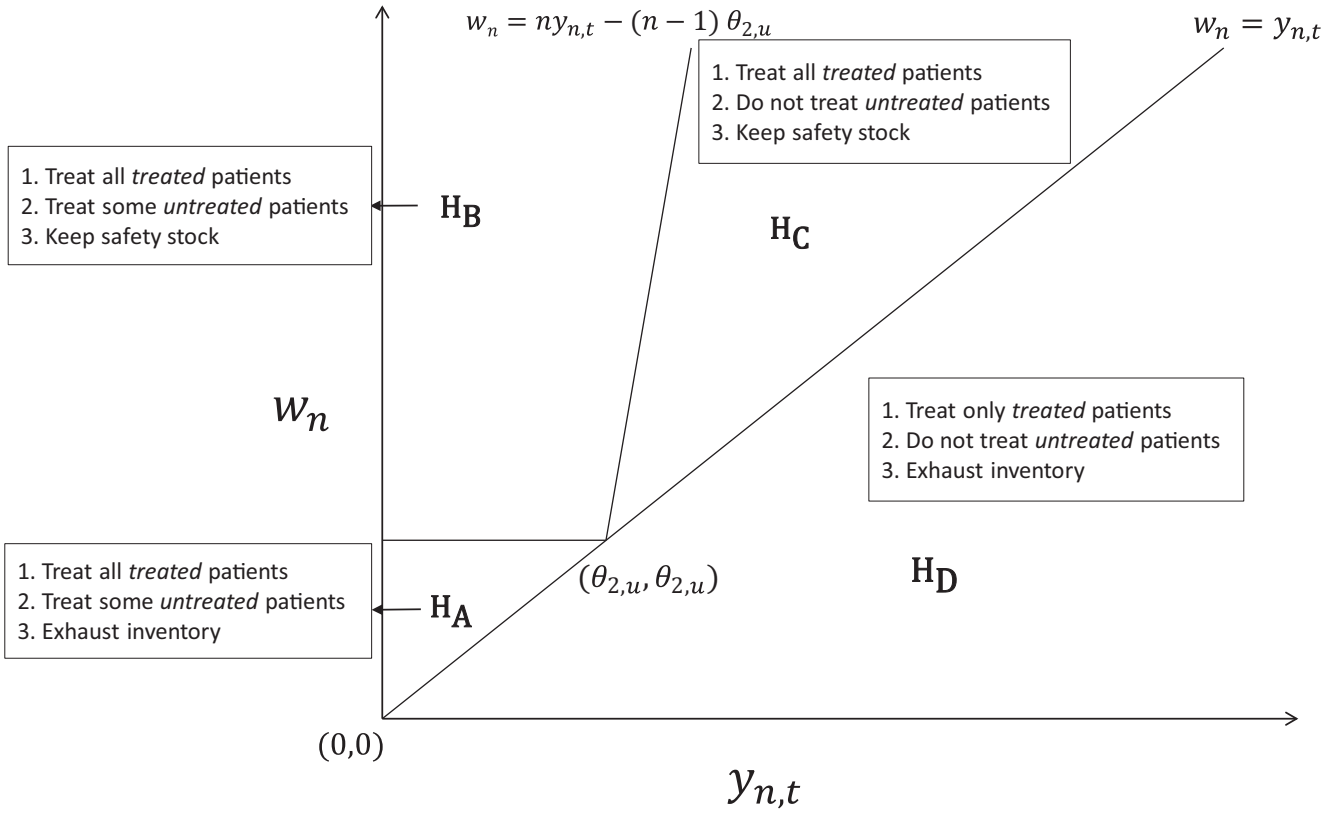
**Figure 5 Characterization of *Two-Period* Heuristic**




$$x^*_{n,t} = \min\{y_{n,t},\ w_n\},$$

$$x^*_{n,u} = \begin{cases} w_n - y_{n,t} & \text{if } y_{n,t} < \min\{w_n,\ \theta_{2,u}\} \ \&\ w_n < \theta_{2,u} \\ \dfrac{w_n + (n-1)\theta_{2,u}}{n} - y_{n,t} & \text{if } w_n \geq \max\{\theta_{2,u},\ ny_{n,t} - (n-1)\theta_{2,u}\} \\ 0 & \text{otherwise.} \end{cases}$$

We conclude this subsection by comparing the structure of the two heuristics. The *Safety-Stock* heuristic is conceptually quite simple but difficult to implement as it requires computation of the optimal value of $A$ numerically. The *Two-Period* heuristic, on the other hand, has a seemingly complex structure but it can be implemented easily as it is characterized by a single threshold which can be computed using a spreadsheet if a user can provide the underlying parameter values.

### 6.3. Upper Bound

Due to the computational challenges involved in calculating the optimal policy through backward induction for longer horizons and intermediate values of $0 < \gamma_t < 1$, we construct a simple perfect information upper bound on the objective function to evaluate and compare the performance of the heuristics (e.g., Bertsekas 1999, Chapter 6). In particular, we generate $K$ sample paths corresponding to realizations of drug supplies over the problem horizon denoted by $\boldsymbol{z}[i] = [z_1[i],\ z_2[i],\ \ldots,\ z_N[i]]$, where $z_n[i]$ is drawn from the distribution $F_n(\cdot)$. We calculate the optimal decisions for the $i$th sample path by solving the following linear program:

$$U^i_N(y_{N,t},\ w_N) = \max_{x_{n,t}[i],\ x_{n,u}[i]\forall n} \sum_{n=1}^{N} (\Delta_{n,t}x_{n,t}[i] + \Delta_{n,u}x_{n,u}[i] + \tilde{\Delta}_{n,t}y_{n,t}[i]) \quad (21)$$

s.t. (3) and

$$x_{n,t}[i] + x_{n,u}[i] \leq w_n[i]\ \forall n$$
$$x_{n,t}[i] \leq y_{n,t}[i]\ \forall n$$

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$$y_{n-1,t}[i] \le x_{n,u}[i] + y_{n,t}[i] - \gamma_t(y_{n,t}[i] - x_{n,t}[i])\ \forall n$$

$$w_n[i] = w_{n+1}[i] - x_{n+1,t}[i] - x_{n+1,u}[i] + z_n[i]\ \forall n$$

$$x_{n,u}[i] \ge 0\ \forall n$$

$$x_{n,t}[i] \ge 0\ \forall n.$$

The upper bound, $U_N(y_{N,t},\ w_N)$, is then calculated as a sample average of $K$ perfect information value functions $U_N^i(y_{N,t},\ w_N)$:

$$U_N(y_{N,t},\ w_N) = \frac{1}{K}\sum_{i=1}^{K} U_N^i(y_{N,t},\ w_N). \tag{22}$$

## 7. Numerical Illustrations

In this section, we evaluate the performance of the two heuristics using the objective value measured in QALYs and understand how it is affected by the magnitude of supply uncertainty and the coefficient of resistance. We divide our numerical experiments in two parts: (i) comparison of upper bound with the optimal policy (section 7.2) for small-sized problems and (ii) comparison of the heuristics with the upper bound (section 7.3) for large-sized problems. We begin by describing the parameter values used in the numerical experiments (section 7.1).

### 7.1. Parameter Values

To the extent possible, we base our parameter values on published literature and vary them over reasonable ranges to conduct sensitivity analysis. All parameter values and their corresponding sources are listed in Table 5.

As noted earlier (section 5), we restrict our numerical experiments to nontrivial cases, that is, $\bar{q}_t > \underline{q}_t,\ q_u > q_r$. Since the QOL utility values reported in the literature depend on the underlying health state of the patients, which is determined by a combination of the CD4+ count and viral load, we make certain assumptions to map them onto the treatment categories as required in our model.

As per WHO guidelines for resource-limited settings, patients become eligible for ART when the CD4+ count drops below 350 cells per cubic millimeter (WHO 2016). Hence, we assumed that the *untreated* patients have an average CD4+ count of 200–350 cells per cubic millimeter. We estimated the QOL utility for these patients ($q_u$) to be 0.84 based on the results of a meta-analysis of more than 25 individual studies (Tengs and Lin 2002) and varied it from 0.74 to 0.92 for sensitivity analysis. Furthermore, we assumed that *treated* patients who are sensitive to treatment are asymptomatic and accordingly estimated their QOL utility value ($\bar{q}_t$) to be 0.93 based on the values reported in the literature (Sanders et al. 2005, Tengs and Lin 2002, Weinstein et al. 2001) for asymptomatic patients. Furthermore, we assumed that the QOL utility for *treated* patients who did not receive treatment in a particular period but are still sensitive to treatment to be approximately 10% lower ($\underline{q}_t = 0.83$) than the *treated* patients who are receiving treatment to reflect the effect of short-term treatment interruption. The QOL utility values for patients resistant to treatment was the most difficult to estimate. The typical clinical outcome of failing therapy is rebound of viral load, which then results in rapid decline in CD4+ count and development of opportunistic infections. Some patients might also develop clinical AIDS. Since the range of outcomes is quite large and varied, we used a wide range of estimates and center it around 0.73 for this category.

Oyugi et al. (2007) report that about 13% patients in a HAART program in Uganda developed resistance during prolonged interruption of treatment due to drug shortages. In contrast, Parienti et al. (2008) found that sustained interruptions are more likely to result in failure of therapy than intermittent interruptions stemming from behavioral noncompliance to treatment. Using statistical analysis, they estimated that almost 100% of the patients would fail therapy if

**Table 5 Parameter Values for Numerical Experiments**

| Parameter | Nominal value | Range of values | Source |
|---|---|---|---|
| $\delta$ | 0.99 | – | Shepard and Thompson (1979) and Drummond (1989) |
| $\beta_t$, $\beta_u$, $\beta_r$ | 1 | – | |
| $\bar{q}_t$ | 0.93 | – | Weinstein et al. (2001), Tengs and Lin (2002), and Sanders et al. (2005) |
| $q_r$ | 0.73 | – | Tengs and Lin (2002) and Sanders et al. (2005) |
| $\underline{q}_t$ | 0.83 | – | |
| $q_u$ | 0.84 | {0.74, 0.76, 0.78, 0.80, 0.82, 0.84, 0.86, 0.88, 0.90, 0.92} | Weinstein et al. (2001) and Tengs and Lin (2002) |
| $\gamma_t$ | 1 | {0,0.2,0.4,0.6,0.8,1} | Oyugi et al. (2007), Parienti et al. (2008) |
| $z$ | $U(1,10)$ | {U(1,10), U(2,9), U(3,8), U(4,7), U(5,6)} | Model Assumption |
| $N$ | 24 | {12,18,24} | Model Assumption |

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the interruption lasted about 30 days. Hence we considered the entire range of 0 to 1 for coefficient of resistance $\gamma_t$.

A period in our model is taken to be one month to reflect the typical frequency of shipment of drugs to the clinics. We choose $N = 24$ reflecting a time horizon of 2 years, which is typical of the funding cycles in global health context (Natarajan and Swaminathan 2014). We also consider alternate time horizons of 12 and 18 months in our sensitivity analysis. We set the single period (monthly) discount rate $\delta = 0.99$, which is approximately equivalent to an annual discount rate of 5% (Drummond 1989, Shepard and Thompson 1979). However, due to the short horizon, our results are not sensitive to the actual choice of the discount rate. A meta-analysis of more than 13 cohort studies (Egger et al. 2002) found that the annual mortality rate for HIV patients ranges from 1% to 5% for CD4+ counts of our interest. These correspond to a monthly survival rate of 99.5% to 99.9%. Hence, we assume that the average monthly survival rates $\beta_t$, $\beta_u$ and $\beta_r$ are constant and equal to 1 for ease of computation. The initial *treated* patient pool and the ARV inventory level are set to 0, that is, $y_{N,t} = 0$ and $w_N = 0$, to reflect the situation faced by a new HIV clinic. We do not have access to operational data on the distributions of drug supply received by clinics. Hence, we vary the support of the supply distribution such that the mean is held constant while changing the variability.

### 7.2. Comparison of Upper Bound with the Optimal Policy

In this experiment, we perform simulations to evaluate the tightness of the upper bound. We compute the optimal policy and the upper bound for the parameter values mentioned in Table 5 and measure the tightness of the bound as $T = \frac{QALY_{ub} - QALY_{opt}}{QALY_{opt}}$, where $QALY_{ub}$ is the average QALYs collected over the planning horizon under deterministic supply and $QALY_{opt}$ is the optimal objective function value computed through backward induction. We set the coefficient of resistance, $\gamma_t = 1$ for computational ease and because we observed numerically that the gap between the two is the largest for this case. We use $K = 100{,}000$ sample paths in equation (EC.6.1).

Table 6 shows that the average tightness of the upper bound is below 1.6% for a 12 period problem and below 2.6% for a 24 period problem. In general, the upper bound is tighter for lower values of $q_u$ for a fixed horizon. The reason for this is that optimal solution enrolls fewer *untreated* patients compared to the upper bound solution due to supply uncertainty. The impact of this under-enrollment is lower for higher values of $q_u$. Furthermore, the upper bound is looser for longer problem horizons as the gaps in QALYs due to suboptimal decisions accumulate. These experiments indicate that the upper bound is reasonably close to the optimal policy and hence we use it as a benchmark to compare the performance of our heuristics for large problem sizes, where numerical characterization of the optimal policy is computationally cumbersome.

**Table 6 Tightness of Upper Bound with Respect to Optimal Policy for $\gamma_t = 1$**

| | Tightness | | |
|---|---|---|---|
| $q_u$ | $N = 12$ | $N = 18$ | $N = 24$ |
| 0.74 | 0.71% | 0.88% | 1.08% |
| 0.76 | 0.97% | 1.24% | 1.53% |
| 0.78 | 1.08% | 1.40% | 1.74% |
| 0.80 | 1.15% | 1.51% | 1.88% |
| 0.82 | 1.20% | 1.59% | 1.99% |
| 0.84 | 1.27% | 1.74% | 2.05% |
| 0.86 | 1.32% | 1.82% | 2.15% |
| 0.88 | 1.37% | 1.89% | 2.25% |
| 0.90 | 1.42% | 1.99% | 2.39% |
| 0.92 | 1.52% | 2.15% | 2.59% |

### 7.3. Performance of Heuristics

In this experiment, we first compare the performance of the two heuristics against the upper bound for different values of $q_u$ and $\gamma_t$. We chose to vary these two parameters because their estimates based on the published literature are the least certain. Next, we investigate the impact of supply uncertainty on the performance of the heuristics.

**7.3.1. Impact of the Coefficient of Resistance ($\gamma_t$) and QOL of *Untreated* Patients ($q_u$).** Figure 6a shows that the average performance gap of the *Two-Period* and the *Safety-Stock* heuristics increases with the coefficient of resistance, $\gamma_t$, reflecting that the trade-off becomes progressively more expensive. Furthermore, the performance gap for the *Two-Period* heuristic is slightly greater than that for the *Safety-Stock* heuristic for $\gamma_t = 0$ but is substantially lower for all values of $\gamma_t > 0$. While the latter increases from 2.54% (for $\gamma_t = 0$) to 11.98% (for $\gamma_t = 1$), the former only increases from 3.43% to 3.76%.

Figure 6c shows that both heuristics become increasingly suboptimal (their performance gap increases) for increasing values of $q_u$. This is because, for fixed values of $\bar{q}_t$, $\underline{q}_t$ and $q_r$, higher values of $q_u$ represent cases with higher relative penalty of treatment interruption as *untreated* patients are progressively healthier than patients whose treatment has been interrupted. However, the impact on *Safety-Stock* heuristic is much more substantial whereas the

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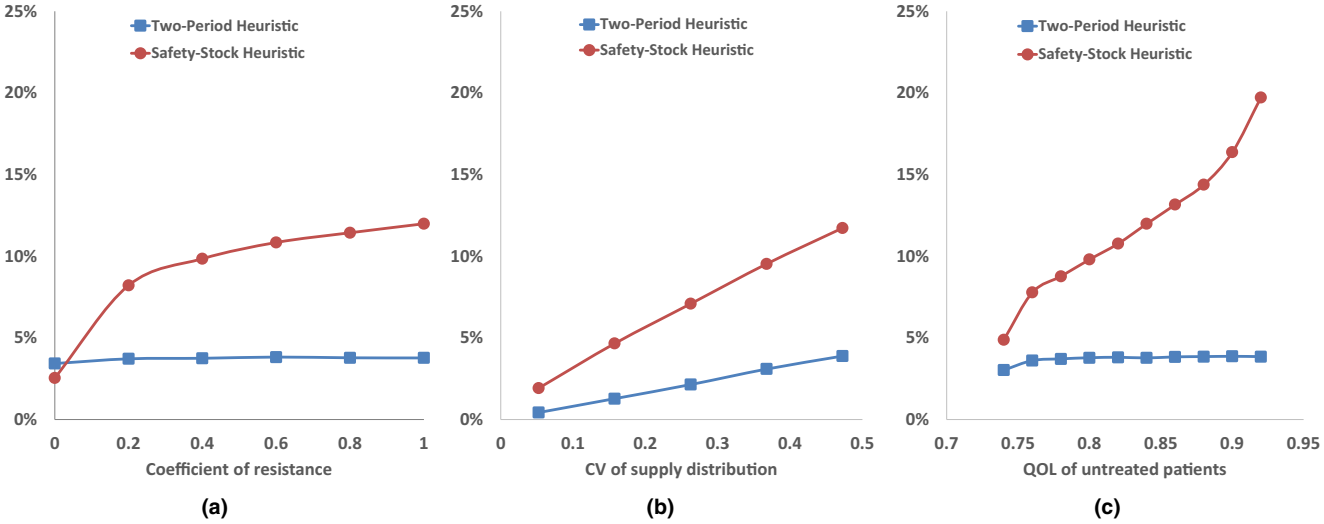
**Figure 6 Comparison of the Performance Gaps of *Two-Period* and *Safety-Stock* Heuristics [Color figure can be viewed at wileyonlinelibrary.com]**




performance of *Two-Period* heuristic is relatively stable over different values of $q_u$.

In summary, from the first experiment, it is noteworthy that the *Two-Period* heuristic is robust to variations in $\gamma_t$ and $q_u$. This is primarily because the value of the threshold in the *Two-Period* heuristic ($\theta_{2,u}$) adjusts based on the changes in the underlying problem parameters ($\gamma_t$ and $q_u$) allowing it to better capture the changes in the underlying trade-off of the decision problem. However, such dependence is not explicitly built into the estimation of the parameter $A^*$ of the *Safety-Stock* heuristic, which depends only on the pool of the *treated* patients.

**7.3.2. Impact of Supply Uncertainty on Heuristics.** To investigate the impact of supply uncertainty on the performance of heuristic, we vary the coefficient of variation of supply distribution by keeping the mean fixed and varying the support of the distribution as described in section 7.1 and shown in Table 5.

Figure 6b shows that the performance of *Safety-Stock* and *Two-Period* heuristic worsens with increase in supply variability. For supply distribution with low variability (CV = 0.05), the average performance gap of *Safety-Stock* and *Two-Period* heuristic is below 2% and 0.5%, respectively. However, for supply distributions with higher variability (CV = 0.47), the performance gap of *Safety-Stock* and *Two-Period* heuristic worsens and is around 12% and 4%, respectively. The *Two-Period* heuristic consistently outperforms the *Safety-Stock* heuristic and the gap between the two is increasingly greater for higher levels of supply uncertainty.

In summary, we note that the performance gap for the *Two-Period* heuristic is consistently below 4% for all realistic combinations of the parameter values considered whereas that for *Safety-Stock* heuristic can be as high as 20%, especially for high values of $q_u$ and $\gamma_t$, that is, when the likelihood and impact of treatment interruption is very high. Furthermore, its performance is much more robust to changes in parameter values compared to that of the *Safety-Stock* heuristic. These observations suggest that a simplified two period problem is able to capture the essence of the dynamic trade-off between enrolling a *untreated* patient now and increasing the risk of not being able to provide uninterrupted treatment to her in the future. On the contrary, the heuristic in which the safety stock depends only on the size of the *treated* patient pool but not the current inventory is unable to do so and hence performs poorly. Finally, it is worth noting that we numerically compute the "optimal" level of safety stock for our experiments, which is unlikely to be the case in practice. Hence, the potential benefit of switching to a *Two-Period* heuristic might be even higher.

REMARK 2. To investigate whether the superior performance of the *Two-Period* heuristic is because of the small scale of the problem, we also conduct experiments under two additional supply distributions, $U(1, 50)$ and $U(1, 100)$. We find that the main qualitative insights remain unchanged: (i) The *Safety-Stock* heuristic becomes increasingly sub-optimal for greater values of $q_u$ and the performance gap increases up to 25% for $U(1, 100)$, and (ii) the performance of the *Two-Period* heuristic is fairly stable for different values of $q_u$ as well as the supply distribution (around 5%). These results imply that the performance of the heuristics depends largely on the CV of the underlying supply distribution; which is nearly

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the same for $U(1,10)$, $U(1,50)$ and $U(1,100)$. For brevity, we report these results in Appendix EC.5.

REMARK 3. In our numerical study thus far, we assumed that the supply distribution is the same throughout the planning horizon. However, in practice, this distribution may vary due to several reasons. In Appendix EC.5, we consider three scenarios, where the distribution of the ARV supply: (i) stochastically decreases over the time horizon, (ii) stochastically increases over the time horizon, and (iii) stochastically decreases for the first half and then increases for the second half of the time horizon. We find that the main insights from our experiments continue to hold: (i) the *Two-Period* heuristic outperforms the *Safety-Stock* heuristic, and (ii) the performance of the *Two-Period* heuristic is robust across the parameter values, whereas the *Safety-Stock* heuristic becomes increasingly sub-optimal for increasing values of QOL of *untreated* patients ($q_u$) and the coefficient of resistance ($\gamma_t$).

## 8. Model Extension

In this section, we extend our modeling framework by introducing heterogeneity in the *treated* patient pool. We create two sub-categories of *treated* patients—*treated-H* and *treated-L*—that differ in their susceptibility to develop resistance upon treatment interruption and the QOL scores. We provide a brief overview of the extended model here and leave the details to Appendix EC.6.

### 8.1. Problem Formulation

Let $y^H_{n,t}$ and $y^L_{n,t}$ denote number of patients in the *treated-H* and *treated-L* pool in period $n$, respectively, who are still responsive to first-line treatment. Let $\beta^H_t$ and $\beta^L_t$ denote the survival probabilities of the patients in the *treated-H* and *treated-L* pool, respectively. Let $\gamma^H_t$ and $\gamma^L_t$ denote the coefficients of resistance of the patients in the *treated-H* and *treated-L* pool, respectively. We assume that $0 \le \gamma^H_t \le \gamma^L_t \le 1$ which implies that the patients in the *treated-H* pool have lower propensity to develop resistance compared to patients in the *treated-L* pool.

At the beginning of period $n$, the clinic decides to treat $x_{n,u}$ *untreated* patients, $x^H_{n,t}$ of the $y^H_{n,t}$ *treated-H* patients, and $x^L_{n,t}$ of the $y^L_{n,t}$ *treated-L* patients. Of the remaining $(y^H_{n,t} - x^H_{n,t})$ *treated-H* patients who remain untreated in current period, a fraction $\gamma^H_t$ develop resistance to first-line treatment, a fraction $p_{HL}(1-\gamma^H_t)$ transition to the *treated-L* pool, where $p_{HL} \in [0,\ 1]$, and a fraction $p_{HH}(1-\gamma^H_t)$ remain in the *treated-H* pool, where $p_{HH} = 1 - p_{HL}$. Thus, the number of *treated-H* patients in the beginning of period $n-1$ is given by:

$$y^H_{n-1,t} = \beta^H_t(x_{n,u} + x^H_{n,t} + (1-\gamma^H_t)(y^H_{n,t} - x^H_{n,t})p_{HH}). \quad (23)$$

Similarly, of the remaining $(y^L_{n,t} - x^L_{n,t})$ *treated-L* patients who remain untreated in the current period, a fraction $\gamma^L_t$ develop resistance to the first-line treatment and the remaining $(1-\gamma^L_t)$ fraction of the patients remain in the *treated-L* pool. For simplicity, we assume that none of the patients from the *treated-L* pool transition to the *treated-H* pool, that is, $p_{LH} = 0$ and $p_{LL} = 1$. Then, the number of *treated-L* patients in the beginning of period $n-1$ is given by:

$$y^L_{n-1,t} = \beta^L_t(x^L_{n,t} + (1-\gamma^L_t)(y^L_{n,t} - x^L_{n,t}) + (1-\gamma^H_t)(y^H_{n,t} - x^H_{n,t})p_{HL}). \quad (24)$$

Note that by setting $p_{HL} = 0$ and $p_{HH} = 1$, the extended model collapses to our main model (as none of the patients from the *untreated* pool transition to the *treated-L* segment and thus *treated-H* segment collapses to the *treated* segment).

We modify the notation of the original model to accommodate the extended state space and use $\mathbf{x}_n := [x_{n,u},\ x^H_{n,t},\ x^L_{n,t}]$ to denote the decision vector, $\mathbf{y}_n := [y_{n,i},\ y_{n,u},\ y^H_{n,t},\ y^L_{n,t},\ y_{n,r}]$ to denote the number of patients in each segment, and $h_n(\mathbf{x}_n,\ \mathbf{y}_n)$ denote the reward collected by the clinic at the end of period $n$. Then, the clinic's decision problem in this extended model can be stated as:

$$\max_{\mathbf{x}_n} \mathbb{E}\left[\sum_{n=1}^{N} \delta^{N-n} h_n(\mathbf{x}_n, \mathbf{y}_n)\right]$$
$$\text{s.t. } (1), (2), (23), (24), (EC.12), (EC.13), \quad (25)$$

$$x^H_{n,t} + x^L_{n,t} + x_{n,u} \le w_n \ \forall n, \quad (26)$$

$$0 \le x^H_{n,t} \le y^H_{n,t} \ \forall n, \quad (27)$$

$$0 \le x^L_{n,t} \le y^L_{n,t} \ \forall n, \quad (28)$$

$$0 \le x_{n,u} \le y_{n,u} \ \forall n. \quad (29)$$

As in our main model, the dynamics of the problem allows us to reduce the state space and reformulate the decision problem of the clinic as a dynamic programming problem (see Equation (EC.14) in Appendix EC.6).

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### 8.2. Adjusted Heuristics and Numerical Performance

The expanded state space makes the characterization of the optimal policy for the extended model formulation more difficult than that for the original model. Hence, we employ extensive numerical experimentation to assess the robustness of our insights from the main model in this setting. Toward this end, we adjust our two heuristics – *Safety-Stock* and *Two-Period* —to incorporate the additional features of our extended model and evaluate their performance with respect to a suitably modified upper bound (see Appendix EC.6.1). For ease of comparison with the results of the original model, we replicate the design of numerical experiments from section 7 with some changes required due to the additional parameters involved in the extended model formulation. All parameter values used in this numerical analysis are described in Table EC.3 in Appendix EC.6. For brevity, we only report the results for extreme values of the coefficients of resistance, namely $\gamma_t^H$ and $\gamma_t^L$ but our analysis confirms that the results are similar for intermediate values.

**Adjusted Safety-Stock Heuristic**: This heuristic first prioritizes the treatment of patients in the *treated-H* pool followed by the treatment of patients in the *treated-L* pool. Thus, for period $n$, we have $x_{n,t}^H = \min\{y_{n,t}^H,\ w_n\}$ and $x_{n,t}^L = \min\{(w_n - y_{n,t}^H)^+,\ y_{n,t}^L\}$.

Similar to the *Safety-Stock* heuristic in our main model (section 6.1), new patients from the *untreated* pool are enrolled in the program such that the safety stock carried to the next period is proportional to the number of *treated-H* and *treated-L* patients in the next period. The proportionality constant is denoted by $A$. Thus, it can be shown that the number of *untreated* patients to enroll in period $n$ is:

$$x_{n,u} = \begin{cases} w_n - y_{n,t}^H - y_{n,t}^L & \text{if } y_{n,t}^H + y_{n,t}^L < \min\{w_n,\ \tilde{\theta}_{2,u}\} \ \&\ w_n < \tilde{\theta}_{2,u} \\ \dfrac{w_n + (n-1)\theta_{2,u}}{n} - y_{n,t}^H - y_{n,t}^L & \text{if } w_n \geq \max\left\{\tilde{\theta}_{2,u},\ n\left(y_{n,t}^H + y_{n,t}^L\right) - (n-1)\tilde{\theta}_{2,u}\right\} \\ 0 & \text{otherwise.} \end{cases}$$

**Adjusted Two-Period Heuristic**: To account for the newly introduced patient sub-segments, we modify the parameter $\theta_{2,u}$ in the *Two-Period* heuristic by replacing $\Delta_{1,t}$ with $\Delta_{1,t}^H$ and $\tilde{\Delta}_{1,t}$ with $\tilde{\Delta}_{1,t}^H$, where $\Delta_{1,t}^H$ and $\tilde{\Delta}_{1,t}^H$ are as defined in Appendix EC.6. This ensures that when the extended model collapses to our main model, the *Adjusted Two-Period* heuristic coincides with the *Two-Period* heuristic. Thus, $\tilde{\theta}_{2,u} = F^{-1}\left(1 + \frac{\Delta_{2,u} + \delta(\tilde{\Delta}_{1,t}^H - \Delta_{1,t}^H)}{2\delta(\Delta_{1,t}^H - \Delta_{1,u})}\right)$. Furthermore, to reflect the prioritization of the *treated-H* pool over that of patients in *treated-L* group, we have $x_{n,t}^H = \min\{y_{n,t}^H,\ w_n\}$ and $x_{n,t}^L = \min\{(w_n - y_{n,t}^H)^+,\ y_{n,t}^L\}$.

Finally, to determine the number of *untreated* patients to enroll, we simply adjust the *Two-Period* heuristic by replacing $y_{n,t}$ with $(y_{n,t}^H + y_{n,t}^L)$. Thus, we have:

$$x_{n,u} = \left(\frac{w_n - x_{n,t}^H\left(1 + A\gamma_t^H\right) - x_{n,t}^L\left(1 + A\gamma_t^L\right) - Ay_{n,t}^H\left(1 - \gamma_t^H\right) - Ay_{n,t}^L\left(1 - \gamma_t^L\right)}{1 + A}\right)^+.$$

Figure 7a (resp., Figure 7d) shows that the *Adjusted Two-Period* heuristic outperforms the *Adjusted Safety-Stock* heuristic for all values of $\gamma_t^H$ (resp., $\gamma_t^L$). Figure 7b and e shows that the performance of both the heuristics worsen with increase in supply uncertainty. However, the *Adjusted Two-Period* heuristic consistently outperforms the *Adjusted Safety-Stock* heuristic. Figure 7c and f shows that both the heuristics become increasingly sub-optimal for increasing values of $q_u$. Again, for all the parameter values, the *Adjusted Two-Period* heuristic performs better than *Adjusted Safety-Stock* heuristic.

These results demonstrate that the performance of *Adjusted Two-Period* and *Adjusted Safety-Stock* heuristics for the extended model is similar to that of *Two-Period* and *Safety-Stock* heuristics, respectively, for the original model. In other words, the insights obtained for the original model are robust to inclusion of heterogeneity in treated patient pool.

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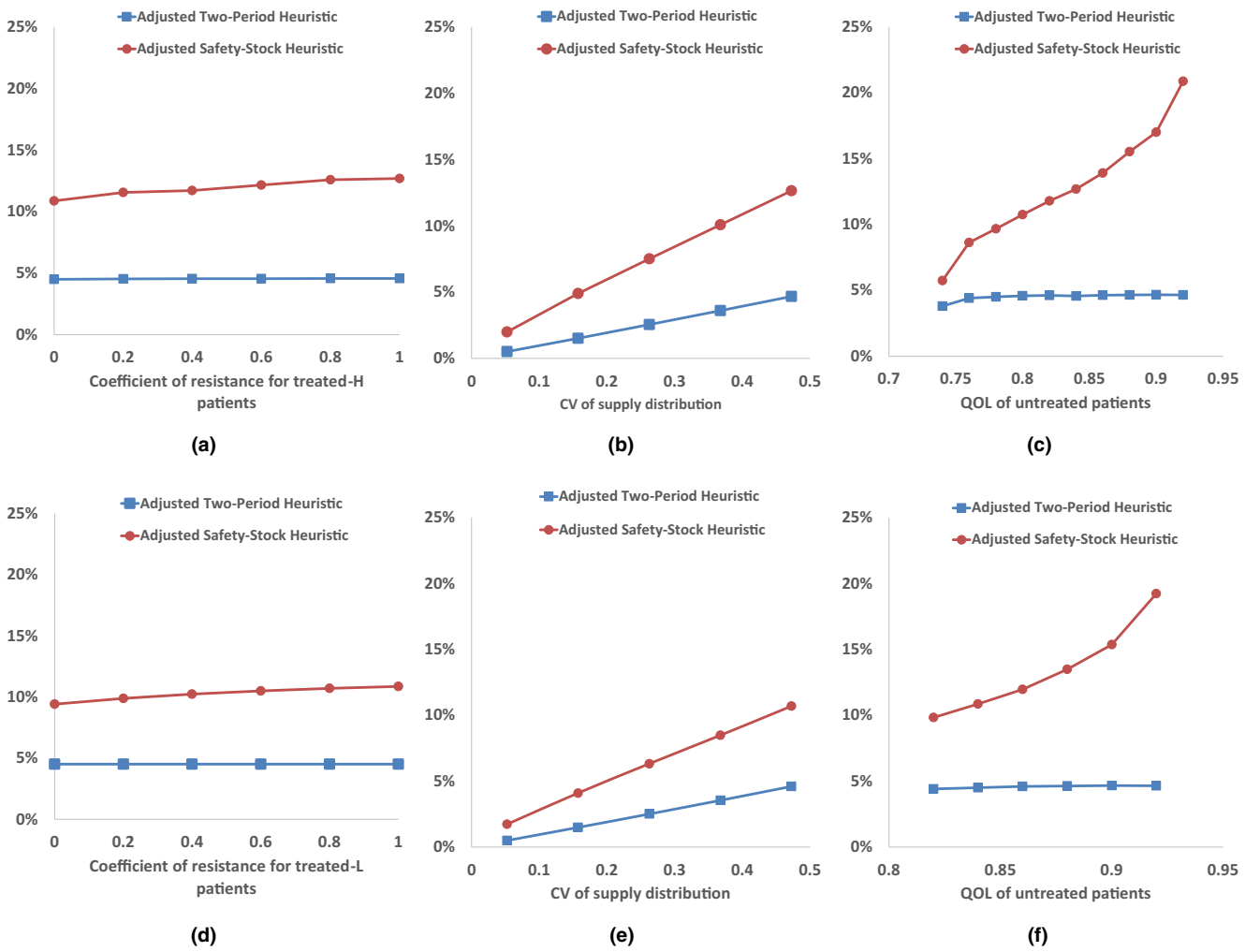
**Figure 7** **Comparison of the Performance Gaps of *Adjusted Two-Period* and *Adjusted Safety-Stock* Heuristics. In the Top Panel, $\gamma_t^L = 1$. In Addition, $\gamma_t^H = 1$ in Figure 7b and c. In the Bottom Panel, $\gamma_t^H = 0$. In Addition, $\gamma_t^L = 1$ in Figure 7e and f [Color figure can be viewed at wileyonlinelibrary.com]**




## 9. Conclusions

In this study, we develop a parsimonious model, which captures the fundamental trade-off faced by HIV clinics in resource-limited settings arising from limited and uncertain supply of drugs. Unlike previous qualitative discussions on ARV rationing in the literature, our model is more suitable for operational planning decisions at the clinic level as it accounts for the inventory level and the size of *treated* patient pool. Despite making simplifying assumptions, the analytical structure of the optimal policy is too complex to be used in practice. Furthermore, its structure presents an important ethical dilemma: under some conditions, it is optimal to deny treatment to the pool of *treated* patients to safeguard against future treatment interruptions, Hence, we leverage other key structural properties of the optimal policy to design a simpler heuristic that performs much better than those employed in practice over a wide range of realistic parameter values. Finally, we show that these numerical insights continue to hold for an extended model with heterogeneity in the *treated* patient pool (along the dimensions of QOL and susceptibility to develop resistance).

In practice, any decision related to treatment rationing at the operational level is intricately linked to other aspects of the HIV epidemic such as clinical guidelines on eligibility and impact of treatment on prevention. Deo (2007) presents a framework for broader issues involved in treatment scale-up including how treatment, prevention and diagnoses are interlinked via patient behavior and disease epidemiology. However, here we focus only on the impact of supply uncertainty on the aggregate health outcomes of HIV-positive patients for a given set of clinical

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eligibility guidelines as a starting point since it has not been studied before. We believe that the insights generated from our analysis, in turn, can be used to build a simulation model that can allow for more detailed disease dynamics and a more accurate calculation of the QALYs for various enrollment policies.

Beyond the immediate context of HIV treatment in resource-limited settings, our model contributes to the vast literature on inventory rationing by explicitly modeling the impact of past service decisions on customer dynamics across segments. This effect is applicable to organizations with limited and uncertain availability of a key resource that strive to attain a balance between expanding services to new customers/beneficiaries and avoiding disruption for existing customers/beneficiaries. Examples of such organizations include non-profits that depend exclusively on donations and startups facing funding uncertainty in the initial phase of their lifecycle. Of course, our model may need to be adapted suitably to include other contextual features in addition to this core trade-off and may lead to additional insights beyond the ones presented here.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix:** Proofs of Theoretical Results.

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