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Cost Considerations in the Current ARV Era

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Summary

Of five commonly prescribed regimens for treatment-naïve HIV patients in one clinic (2007–2012), Emtricitabine and Tenofovir with Efavirenz and Raltegravir were the only consistently cost-effective options; the Rilpivirine-based regimen was valuable in limited scenarios. Further data on the comparative effectiveness of Efavirenz and Rilpivirine are needed before they are abandoned.

Introduction

Antiretroviral therapy (ART) has improved morbidity and mortality for persons living with HIV (PLWH)[1]. Currently, there are many effective regimens for treatment-naïve PLWH [2]. In addition to efficacy, antiretroviral (ARV) durability, defined as the time from regimen initiation to discontinuation, has been associated with improved clinical outcomes [3]. Durability was adopted early in the ART era as an indirect measure of effectiveness and tolerability.

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Author Contributions: Dr Eaton is first author on this project and took the lead on study design, analysis, interpretation of results and publication. Dr Tamhane is a biostatistician who performed analysis on ARV regimen durability for this cost-effectiveness analysis. Dr Mugavero assisted in study design, interpretation of results and publication. Dr Saag was integral in interpretation of results and publication. Dr Kilgore is an expert in cost-effectiveness analysis and helped with study design, analysis of cost-effectiveness, interpretation of results and publication.

Perceptions of ART durability and preferred regimens are ever changing. Efavirenz has fallen from favor following reports of increased suicidality in clinical trials [4, 5]. Similarly, Rilpivirine, the backbone of a once preferred single-tablet regimen, is now known to have limited efficacy in those with a high HIV RNA viral load. Due to these limitations and the availability of alternative, tolerable options, Efavirenz (Atripla®) and Rilpivirine (Complera®) are no longer recommended as first-line therapy for treatment-naïve PLWH[6]. Both were downgraded to the "alternative" category by the 2015 Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Of note, the striking number of Efavirenz-related suicidality events reported in mostly open-label clinical trials was not reproduced in large observational studies [7, 8]. With increasing ART options and an evolving treatment landscape, understanding comparative effectiveness is essential.

ART is cost-effective, but it is costly and constitutes over 70% of comprehensive HIV health care expenses [9, 10]. Recently, the DHHS asked providers to educate themselves on ARV costs and generic ARV availability[6]. Nonetheless, the five regimens recommended for treatment-naïve patients, according to the DHHS panel, include the most expensive, least cost-effective options [6, 11, 12]. Alternatively, Atripla® and Complera,® both downgraded to "alternative" options, have been shown to be the most cost-effective options [12, 13]. Although there is a growing demand for cost-conscious HIV care, there is little data on relative cost-effectiveness of contemporary ARV regimens, and current guidelines do not incorporate cost considerations in the selection of preferred treatment regimens. We, therefore, analyzed the cost and utility of contemporary ARV regimens in a real-world, clinical setting.

Methods

This is a cost-effectiveness analysis of 5 ARV regimens incorporating durability and monthly medication costs from the clinic perspective. Although durability is not widely used in cost-effectiveness analyses, it is used often in comparative effectiveness research of HIV treatment[14, 15]. Regimens and durability data were obtained from an observational cohort at the 1917 Clinic, the University of Alabama at Birmingham (UAB)-affiliated HIV clinic serving more than 3,000 PLWH. The UAB 1917 Clinic Cohort database was queried for treatment-naïve patients initiating ARV (≥ 3 drugs) for at least 14 days between January 1, 2007 and December 31, 2012. Pregnant patients were excluded. A total of 546 patients were eligible, but analysis was restricted to patients initiating one of the following: Emtricitabine and Tenofovir in combination with Efavirenz, with Raltegravir, with Ritonavir and Darunavir, with Ritonavir and Atazanavir, or with Rilpivirine as they represented 90% of prescriptions to treatment-naïve patients during the study period. The study was approved by the UAB Institutional Review Board.

Effectiveness

Durability was defined as time from ART regimen initiation to discontinuation, regardless of reason for discontinuation. Any change in ART lasting more than 14 days was considered discontinuation. Switching from individual drugs to a fixed-dose combination (FDC) of the

same constituent drugs was not considered discontinued. Patients were censored after their last contact with the clinic, death or end of follow-up period (December 2014), whichever came first. If a patient was lost to follow up prior to regimen discontinuation, their regimen was considered discontinued 6 months from their last HIV provider visit, as typically patients are given six refills per visit.

ARV Cost

The cost of a 30-day supply of each regimen was calculated using the average 340 b pricing provided by four national wholesale pharmacies[16]. The 340b Drug Discount Program, a federal program for those serving vulnerable and low-income patients, requires manufacturers provide reduced prices to eligible healthcare institutions[16]. The 1917 Clinic is eligible for 340b pricing.

Statistical Analysis

Median durability (months) was obtained from the Kaplan-Meier survival curves. The Incremental Cost Effectiveness (ICER) of each regimen was calculated by comparing each regimen to the next most costly regimen. An ideal regimen will have a low ICER: for a minimal additional cost it provides greater durability.

Sensitivity Analysis

Several sensitivity analyses were performed. First, cost inputs were varied using a regional 340b vendor price, Average Wholesale Price (AWP), and Market Price (MP)[6]. Then, durability was adjusted for each regimen using mean months of durability +/− 1 standard deviation (SD). Third, durability was adjusted for those lost to follow up (N=117): a) date of loss to follow up was considered the discontinuation date b) date of loss to follow up plus 3 months was considered discontinuation date. An additional analysis excluded those lost to follow up.

Results

Overall, 491 patients met inclusion criteria. Mean age was 36 years (SD=11 years), 83% were male, and 61% were African American. Median relative durability was lowest for ritonavir-boosted Atazanavir (31.9 mos), followed by Rilpivirine (36.3 mos) and Efavirenz (40.1 mos), while greatest for ritonavir-boosted Darunavir and Raltegravir (47.8 mos) (Table 1). Although regimen costs varied by price index, Efavirenz and Rilpivirine-based regimens were consistently the least expensive (Tables 1 and 2).

Base Case Analysis

ICER was first calculated using the base case: median durability of all patients and average 340b pricing. All regimens were dominated, meaning less durable and more costly, when compared with the Efavirenz and Raltegravir-based regimens. This pattern was consistent regardless of the pricing index. The incremental cost of Raltegravir per additional month of durability relative to Efavirenz was $47 with a range of $46 to $56 (table 2) depending on price index. When using MP and AWP, the Rilpivirine-based regimen was also cost

effective. The incremental cost of Efavirenz per additional month of durability relative to Rilpivirine was $6 and $23 based on MP (table 2) and AWP, respectively.

Sensitivity Analyses

When durability decreased (−1SD) in sensitivity analysis, there was more variability in ICER by price index, but Atazanavir and Darunavir were consistently dominated. As durability increased (+1SD), Efavirenz and Rilpivirine-based regimens were the only consistently valuable options. When varying the date of discontinuation for patients lost to follow up (0, 3 mos as described above) and when excluding those lost to follow up, all regimens were dominated other than Efavirenz and Raltegravir; Rilpivirine became a valuable option when using MP (table 2) and AWP. When excluding those lost to follow up, the incremental cost per month of durability for Raltegravir relative to Efavirenz ranged from $177 to $216. The incremental cost of Efavirenz per additional month of durability relative to Rilpivirine was $2 and $7, using MP and AWP, respectively.

Discussion

With the release of the 2015 DHHS Guidelines came significant changes to first-line HIV treatment recommendations: Atripla® and Complera® lost their position among preferred regimens and were replaced by newer, more expensive options including Dolutegravir, Raltegravir, Triumeq® and Stribild.® Newly-recommended regimens range from $100 to $900 more per patient per month when compared to Atripla® and Complera®[6]. The price differences are challenging to reconcile; these same guidelines include a section on cost considerations, which states that providers should incorporate costs into decision-making and prescribing practices.

Our study incorporates the durability and cost of 5 contemporary ART regimens. Two of these, Darunavir and Raltegravir-based regimens, are currently recommended, but the Efavirenz (Atripla®), Rilpivirine (Complera®), and Atazanavir-based regimens are not. All other regimens were consistently dominated, meaning less durable and more costly, relative to the Efavirenz and Raltegravir-based regimens. The Rilpivirine and Efavirenz-based regimens were consistently least expensive across all pricing indices, but the Rilpivirine was only a cost-effective option when MP and AWP pricing data were used. Despite widely-reported CNS toxicities, the Efavirenz-based regimen was quite durable in our population (median 40.1 mos)[4, 17, 18]. This longevity and inexpensive price ($710.64) made it one of the most cost-effective options. Only Raltegravir and Darunavir-based regimens offered greater durability (47.8 mos). Given the higher price of the Raltegravir-based regimen ($1075.03), the incremental cost was $47 per additional month of therapy relative to the Efavirenz-based regimen. In other words, selection of Raltegravir over Efavirenz for initial treatment will provide roughly 1 more month of durability at an additional cost of $47 per patient per month over the course of treatment. If the Raltegravir, Darunavir or newer Dolutegravir-based regimens are consistently chosen over Efavirenz following treatment guidelines, the HIV drug-related costs will increase tremendously with potentially limited benefit.

Notably, the Raltegravir-based regimen is the only recommended regimen that is twice daily as opposed to once daily. In our analysis, Raltegravir was more durable than all once daily regimens except Darunavir. It is also less expensive than the Dolutegravir and Darunavir-based regimens, both of which are recommended as first line. Whether most providers select one of these once daily regimens over Raltegravir, despite them being more costly options, remains to be seen.

This study was conducted in a single academic center with a moderate sample size; however, the findings were reproduced in multiple sensitivity analyses. Durability has not been used in cost-effectiveness analysis of ARV regimens but is a commonly used comparative effectiveness metric for ARV therapy. It is reassuring that the relative durability of regimens in our study is consistent with published data[19]. Costs vary widely across vendors, payers and calendar year. Trends in relative cost-effectiveness of each of the 5 regimens, however, were unchanged regardless of pricing indices. An ideal assessment would incorporate utility and cost of all recommended regimens (Dolutegravir and Triumeq®), but data is limited due to their recent release.

Conclusion

Although Atripla® and Complera® are not ideal for all patients, they likely still have a role in the current HIV treatment era. Following changes in treatment guidelines, however, many clinicians have abandoned both regimens in treatment-naïve patients. Our study demonstrates that Efavirenz is durable and cost-effective. The Raltegravir-based regimen was the only additional cost-effective option, offering greater durability at an additional cost of $47 per month of therapy. Further ARV cost-effectiveness analysis is essential and should be incorporated into guidelines to optimize care and control rising healthcare costs. The association between Efavirenz and CNS toxicity, which was not evaluated in this study, should be further studied in observational settings before we discard this treatment altogether.

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Table 1

Prescribing Patterns, Durability, Regional 340b Pricing and Average Wholesale Price for 5 Common Regimens

Regimen	N (%)[a]	Median (mos)[IQR]	Regional 340b Price[b]	Average Wholesale Price
Emtricitabine, Tenofovir, Efavirenz	277 (51)	40.1 [12.6,77.5]	$726.26	$2551.99
Emtricitabine, Tenofovir, Rilpivirine	30 (5)	36.3 [17.4, *]	$917.50	$2463.37
Emtricitabine, Tenofovir, ritonavir/ Atazanavir	48 (9)	31.9 [16.6,58.6]	$1070.88	$3369.22
Emtricitabine, Tenofovir, Raltegravir	75 (14)	47.8 [22.6, *]	$1080.6	$2985.24
Emtricitabine, Tenofovir, ritonavir/Darunavir	61(11)	47.8 [25.5, *]	$1153.00	$3358.29

[a] Percentage refers to the percent of those receiving the specific treatment regimen out of 546 eligible patients

[b] Regional 340b price is the actual acquisition cost charged to our clinic for the purchase of specific regimens

* Note: The 75th percentile could not be estimated as the "event" percentage did not reach 75%

Definitions: ICER, Incremental Cost-Effectiveness Ratio, is calculated by comparing the difference in the cost divided by the difference in effect Durability defined as Median Durability from Kaplan-Meier Survival Curves

Table 2

ICER for 5 Common Regimens Using Average 340b Pricing (base case scenario) and Average Wholesale Price (sensitivity analysis)

Regimen	**Median(mos)**	**Average 340b Price[a]**	**ICER (340b Price/mos)**
Emtricitabine, Tenofovir, Efavirenz	40.1	$710.64	Reference
Emtricitabine, Tenofovir, Rilpivirine	36.3	$957.72	Dominated
Emtricitabine, Tenofovir, ritonavir/ Atazanavir	31.9	$1060.35	Dominated
Emtricitabine, Tenofovir, Raltegravir	47.8	$1075.03	$47.32
Emtricitabine, Tenofovir, ritonavir/Darunavir	47.8	$1166.07	Dominated
Regimen	**Median(mos)**	**Market Price**	**ICER (Market Price/mos)**
Emtricitabine, Tenofovir, Rilpivirine	36.3	$2633.34	Reference
Emtricitabine, Tenofovir, Efavirenz	40.1	$2658.24	$6.55
Emtricitabine, Tenofovir, Raltegravir	47.8	$3091.49	$56.27
Emtricitabine, Tenofovir, ritonavir/Darunavir	47.8	$3464.54	Dominated
Emtricitabine, Tenofovir, ritonavir/ Atazanavir	31.9	$3475.47	Dominated

[a]Average 340b Price is the average of four national wholesale pharmacies who provide discounted drugs via the 340b Prime Vendor Program

Definitions: ICER, Incremental Cost-Effectiveness Ratio, is calculated by comparing the difference in the cost divided by the difference in effect Dominated means that a treatment is less durable and more costly than the regimen in the preceding row