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EDITORIAL

Incremental haemodialysis and residual kidney function: more and more observations but no trials

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WHY IS IT SO IMPORTANT TO PRESERVE RESIDUAL KIDNEY FUNCTION?

Residual kidney function (RKF) may confer many benefits to patients with end-stage kidney disease on maintenance dialysis including associations with better patient survival and health-related quality of life [1]. RKF in dialysis patients plays important roles in fluid and salt removal, effective phosphorus excretion, middle molecule clearance, and endogenous vitamin D and erythropoietin production [2–4]. There is increasing evidence to suggest that clearance of some uraemic solutes, particularly middle molecules such as β_2-microglobulin, is highly dependent on RKF. This extends even to very low levels of RKF: patients with renal urea clearance (Kru) of <0.5 mL/min have significantly higher serum β_2-microglobulin levels than those with values between 0.5 and 1 mL/min [5]. Furthermore, residual renal tubular function may represent important removal pathways for these and other compounds, such as hippurate, phenylacetylglutamine, indoxyl sulphate and *p*-cresol sulphate [6, 7].

Loss of RKF is linked to decreased survival [8, 9], likely from poorer uraemic solute clearance [8], volume and blood pressure control [10, 11], higher erythropoietin requirements [12], more inflammation [8] and higher left ventricular mass [13]. The benefits of preserving Kru appear to be greater that one would expect from simply enhanced small solute clearance: a multivariate survival analysis of patients on incremental haemodialysis (HD) suggested that 1 mL/min of Kru resulted in greater survival benefit compared with 1 mL/min of dialysis urea clearance (Kd), possibly due to greater removal of middle molecules by native kidneys and improved volume control [10]. Finally, the available literature suggests greater preservation of RKF with infrequent dialysis [14–17].

HOW CAN WE MEASURE RKF IN DIALYSIS PATIENTS?

The first key question is: how can we measure RKF in dialysis patients? Traditionally, renal function is expressed as glomerular filtration rate (GFR). RKF in the setting of dialysis can be assessed in different ways: (i) Kru, which slightly underestimates GFR due to tubular reabsorption; (ii) creatinine clearance (CrCl), which it overestimates GFR due to tubular secretion; and (iii) composite clearance (Kru + CrCl), which is used in clinical practice with the assumption that tubular function mirrors GFR [18]. Thus, although 24-h urine collections remain the standard method for estimating RKF, the question arises: which clearance is most important in patients on dialysis, Kru, the composite Kru and CrCl, or CrCl? As renal function declines, there is a relative change in the balance between tubular creatinine secretion and GFR; similarly, some other tubular functions, such as the clearance of protein-bound azotaemic toxins, are relatively preserved at reduced levels of GFR [18]. To overcome such difficulties, other markers of filtration have been advocated such as pre-dialysis plasma levels of cystatin C [19, 20], β_2-microglobulin [20, 21] and β-trace protein [20, 21]. Shafi *et al.* [20] recently developed and validated equations that estimate Kru in dialysis patients from serum β_2-microglobulin, β-trace protein and cystatin C concentrations without requiring urine collection. At the same time, Wong *et al.* [21] developed and validated equations that predict RKF in HD patients using serum β_2-microglobulin and β-trace protein. However, it is unclear whether any of these markers will prove sufficiently accurate in the range of RKF in dialysis patients. Further research is necessary to find alternative inexpensive and easily measured filtration markers that are accurate enough to estimate RKF without the need for urine collections. Until such an alternative is found, the regular monitoring of RKF by periodic urine collections is required to ensure that RKF is being maintained and that dialysis schedules do not require adjustment [22]. RKF is roughly approximated by measuring urine output (UO). While RKF and UO do not measure the same physiologic quantities—the former is a clearance, whereas the latter is just a fluid volume—they are closely related as documented by us very recently [23].

WHY TO CHOOSE INCREMENTAL HD IN INCIDENT PATIENTS?

The majority of HD patients initiate dialysis with a relatively intense thrice-weekly HD (3HD/week) regimen of 3–4 h per

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session, with little individualization of prescription based on RKF or other patient factors [1]. Although the regulatory agencies might consider this HD regimen as 'standard of care' and 'adequate requirement', it is by no means perfect [24]. The 3HD/week regimen has been assumed, until recently, almost as a dogma in the dialysis community [25, 26]. Incredibly, the 3 HD/week schedule has been widely accepted worldwide without ever undergoing any randomized controlled trial (RCT) to examine whether less frequent HD treatments would be inadequate or harmful [27]. The optimal regimen for incident patients is not known. It is plausible that the routine practice of fixed-dose 3 HD/week in incident patients with substantial RKF may be harmful, contributing to an accelerated loss of RKF [28, 29]. Incremental HD is based on the simple idea of adjusting its dose according to the metrics of RKF. Indeed, most patients initiating dialysis have some degree of RKF, often Kru >3 mL/min and UO >500 mL/day. Given the importance of RKF preservation in conservative therapy, it seems a contradiction to ignore the contribution of RKF in incident HD patients. What is important to note is that the challenge of preserving RKF or UO in HD patients has never been taken seriously. The Kidney Diseases Outcomes Quality Initiative (KDOQI) suggests that minimum targets of adequacy of the dialysis dose (K_t/V) may be reduced in those with Kru ≥2 mL/min/1.73 m^2 [30]. The European Best Practice Guidelines (EBPG) recommend measuring RKF in HD patients using the mean of urea and creatinine clearances and offer suggestions to incorporate this into the HD prescription to allow individual adjustments of dialysis prescription to meet minimum dialysis adequacy targets [31]. However, these guidelines do not recommend an incremental transition from less to more frequent HD over time, while, ironically, according to most peritoneal dialysis (PD) guidelines, PD dose should be adjusted upwards parallel to decline in RKF, the preservation of which is a high priority target in PD [27, 32].

The commencement of HD is associated with increased levels of mortality, particularly in the elderly [33]. This early period is associated with frequent episodes of hypotension even in units undertaking longer hours and using slower ultrafiltration rates [34]. Intradialytic episodes of hypotension appear to have deleterious effects on both cardiac [35] and cerebral function [36]. The other organ susceptible to hypotension and often overlooked is the kidney; repeated episodes of intradialytic hypotension are implicated in the loss of RKF, which in turn has a negative impact on UO and greater ultrafiltration requirements, leading to a vicious cycle with progressive renal injury [37]. Aside from end-organ effects, the Dialysis Outcomes and Practice Patterns Study has highlighted the wide variation in time to recovery. Ten percent of all patients took longer than 12 h to recover from a HD session, with an increasing recovery time associated with age and comorbidity [38]. This extended time to recovery associated with the dependence upon transportation to an in-centre HD session means that many patients are left with limited quality time at home. This is reflected in the lower treatment satisfaction in older patients in standard HD compared with assisted PD in the Frail Elderly Patient Outcomes on Dialysis study [39]. Incremental HD has a lower burden of treatment. There appears to be no adverse clinical effects during the first years of incremental HD [40] and when there is significant RKF. The advantages of incremental HD might be particularly important for elderly patients with short life expectancy, where transplantation is not an option [3].

RCTs TESTING INCREMENTAL HD ARE URGENTLY NEEDED

The body of literature on incremental HD is surprisingly small but fast growing, especially in recent years [23]. The literature is without exception observational. There are no RCTs that directly compare standard 3 HD/week with incremental HD [23]. There is good evidence that twice-weekly HD offers outcomes that do not appear inferior compared with standard in-centre 3 HD/week in patients with RKF [41]. Indeed, there is one observational study reporting that for an elderly cohort, there are less frequent episodes of hospitalization with twice-weekly HD [14]. A recent large observational study found that there were no differences in survival rates between patients treated by incremental versus standard HD. However, in patients with UO <600 mL/day and Kru <3 mL/min/1.73 m^2, incremental HD was associated with significantly reduced survival [17]. Furthermore, another recent observational study showed that patients undergoing twice-weekly HD had non-inferior outcomes for mortality and cardiovascular events compared with patients without RKF undergoing 3HD/week. However, patients with RKF undergoing twice-weekly HD had an increased risk of mortality compared with patients with RKF undergoing 3HD/week [42].

It is evident from the published literature [23] that there are no well thought out standardized methods of applying incremental HD in clinical practice. Infrequent regimens are currently being used arbitrarily, with no systematic process for making the decision as to which patients require less dialysis and then escalating dialysis dose appropriately as RKF declines over time [22].

The main reason for the patchy adoption of incremental HD is that it requires a dynamic individualized dialysis prescription, taking renal function into account. However, at the present time, there are no clear standards for including RKF in the dose assessment or prescription. While agreeing that evaluating the adequacy of a dialysis prescription should not rely on a single index, if we were obliged to choose one single marker when evaluating dialysis adequacy in the daily practice or when designing the protocol of a clinical trial, we would have no doubt in choosing urea: not only it is a solute easily measurable in blood, urine and dialysate, but also, above all, the urea kinetic model (UKM) is the HD gold standard because it is the only established tool for assessing and prescribing dialysis [31, 43, 44].

As said, at the present time, no RCT testing incremental HD has yet been published. Actually, we are aware of four RCTs: three of them are ongoing [45–47] and the fourth one is not yet recruiting [48]. Among them, the RCT assessing the security and effectiveness of incremental HD (IHDIP RCT) is enrolling incident patients with a Kru ≥4 mL/min/1.73 m^2 [45]. The scientific novelty of this trial is that the prescription of incremental HD is based on the variable target model (VTM) of the UKM

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we have recently proposed in order to give more clinical weight to Kru when compared with Kd [49] (Appendix A1).

The EUDIAL Working Group of ERA-EDTA is planning to design an RCT in incident HD patients, named 'REAL LIFE', by using the acronym of its whole definition: RandomizEd clinicAL triaL on the effIcacy and saFety of incremental haEmodialysis.

REAL LIFE is a pragmatic, prospective, multicentre, open-label RCT and is investigator-initiated, comparing the intervention arm (incremental HD) with the control arm (standard 3 HD/week). Incident patients will be randomized to one of the two treatment groups in equal proportion. To ensure adequate concealment of allocation, the randomization will be performed using a central computer. Patients will be recruited from dialysis centres located prevalently in Europe. Primary outcome is the preservation of RKF assessed as time to anuria (UO $\leq$100 mL/day). Secondary outcomes are the slope of Kru decline over time, all-cause mortality and significant events, including vascular access failure and associated interventions, cardiovascular events and hospital admissions. The follow-up time will be 24 months. The statistical analysis will be done by means of the intention-to-treat approach. The prescription of incremental HD will be based on the VTM [49] (Appendix A1). VTM allows to start and keep patients on a once-weekly HD schedule if Kru is between 3.0 and 4.5 mL/min/35 L. Once-weekly HD should be possible until Kru falls below 2.5–3.0 mL/min/35 L, that is, a GFR $\approx$4 mL/min/35 L. All patients allocated to the intervention arm will keep on the twice-weekly schedule until Kru falls $<$1.5 mL/min/35 L and afterwards the 3 HD/week schedule must be started. The intervention arm patients (once- and twice-weekly HD schedule) should receive an equilibrated K_t/V (eK_t/V) of about 1.2 per session.

The assessment of the key kinetic parameters will be done by using SPEEDY [50], a spreadsheet prescription tool that uses essentially the same equations used by Solute Solver [51], the software based on the double pool UKM recommended by the 2015 KDOQI guidelines [43]. SPEEDY is freely available at the European Nephrology Portal. The link is https://enp-era-edta.org/174/page/home.

CONCLUSIONS

The optimal regimen for incident patients is not known. It is plausible that the routine practice of fixed-dose 3 HD/week in incident patients with substantial RKF may be harmful, contributing to accelerated loss of RKF. Despite increasing evidence derived from observational studies to support the use of incremental HD, RCTs are lacking and are urgently needed. If the potential benefits of incremental HD will be confirmed by RCTs, then starting dialysis at a full dose will be subjecting patients to unnecessarily long or more frequent treatments for an unnecessarily long time, and at higher cost.

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CONFLICT OF INTEREST STATEMENT

None declared.

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APPENDIX A1

Three methods for calculating clearance in HD in a way that is comparable to continuous renal function have been proposed [52]. All three are clearance calculations in the form of the rate of the mass of urea removed (equal to the mass of urea generated in the body) divided by the blood urea concentration. They are the solute removal index (SRI) [53], the standard K_t/V (stdK_t/V) [54] and the equivalent renal clearance (EKR) [55]. They differ only in the interpretation of concentration in blood and on the method of normalizing for body size [52]. The first to be proposed was SRI [53]; stdK_t/V is calculated in the same way as the SRI, but it uses the average pre-dialysis urea concentration instead of the peak [54]; EKR uses time average urea concentration as the blood concentration and can be expressed in more familiar units of millilitres/minute [55]. Toxicity is more likely to be proportional to the time average concentration than to the peak [56]. In that case, EKR can be normalized for body size using urea distribution volume ($V = 35$ L), which is believed to be identical to the total body water volume [49]. One problem with SRI, stdK_t/V and EKR is that they count renal function quantified by Kru as equal to Kd [52]. The equivalence between Kru and Kd, correctly assumed by the UKM, only means that each millilitre/minute of Kd clears the urea from the blood just as 1 mL/min of Kru does [43, 55, 57]. By no means should such kinetic equivalence imply that 1 mL/min of Kd is clinically equivalent to 1 mL/min of urea clearance provided by the native kidneys.

We suggested an adjustment factor of 2.0 for Kru, implying that, compared with HD with the same Kd, renal function is twice as effective in controlling uraemia [49]. Such adjustment factor of 2.0 for Kru has not yet been tested in clinical studies, but is based on scientifically sound concepts. In fact, as we have shown in our article in dealing with the VTM [49], such a value was the result of the selected minimum and maximum values for the variable total clearance. In short, the first KDOQI guidelines for incremental HD prescription were derived from the adequacy criterion on PD [43], which required the total (dialytic + renal) weekly K_t/V to be about 2.0. We pointed out that the assumption that only the total clearance matters necessarily implies clinical equivalence between renal and dialysis clearances, which is clearly wrong and leads to wrong dialysis prescription. Trying to correct, at least in part, the above mistake, we suggested that a greater weight should be given to Kru by varying the total clearance from a minimum at the start of treatment, in the presence of a significant Kru, to a maximum in the anuric state [49]. Of note, this concept is in agreement with the KDOQI 2015 guidelines stating that 'in patients with significant Kru, the dose of dialysis may be reduced provided Kru is measured periodically to avoid inadequate dialysis' [43]. On this basis, we suggested a hypothetical GFR threshold of about 9 mL/min/1.73 m^2 for considering dialysis initiation for a relatively asymptomatic patient, in agreement with the Initiating Dialysis Early and Late (IDEAL) Study [58] and EBPG [31]. Just below such a threshold GFR, which would correspond to a Kru of about 6 mL/min/35 L, a very low dialysis dose would be needed, which however would increase more and more in the presence of a declining Kru, to reach a maximum when Kru approaches zero [49]. This concept can be applied to both versions of the equivalent continuous clearance, namely the stdK_tV [54] and the EKR [55]. Focusing on the latter, for the sake of simplicity, we can say that it could vary from a minimum value of 6 mL/min/35 L just before the patient starts the renal replacement therapy (EKR = Kru) to a maximum of 12 mL/min/35 L when the patient becomes anuric and receives an eK_t/V of about 1.2 thrice a week. So, when Kru falls from 6 mL/min/35 L to 0, EKR increases from 6 to 12 mL/min/35 L. In other words, each millilitre/minute/35 L of Kru loss is being replaced by 2 mL/min/35 L of the EKR component provided by dialysis (EKRd). So, by selecting a Kru threshold of 6 mL/min/35 L and the maximum EKR of 12 mL/min/35 L in anuria, corresponding to an eK_t/V of about 1.2–1.3 on a 3 HD/week schedule, one gets an adjustment factor of 2.0. The associated 'adequacy line' equation is: EKR target = 12 − Kru. However, one could also select a lower threshold, for instance, a GFR of 6 mL/min/1.73 m^2, corresponding to a Kru of about 4 mL/min/35 L, and a maximum EKR of 10 mL/min/35 L, corresponding to an eK_t/V of about 1.05. In this case, the adjustment factor for Kru becomes 10/4 = 2.5. The associated 'adequacy line' equation is now: EKR target = 10 − 1.5 * Kru.

In short, as Kru becomes 4, 3, 2, 1 and 0 mL/min/35 L, the EKR target will be 4.0, 5.5, 7.0, 8.5 and 10 mL/min/35 L,

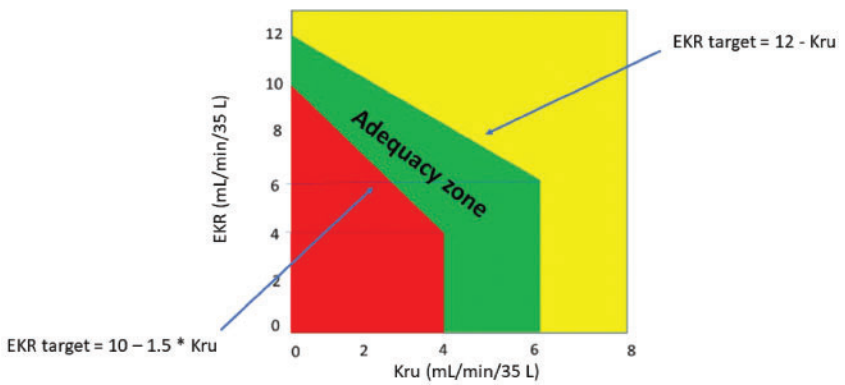

FIGURE A1: Adequacy map for the prescription of incremental HD based on the chosen total EKR target: on one side (right side of the figure), the 'above target' EKR is shown; on the opposite side (left side of the figure), the 'below target' EKR is shown (potential risk of under-dialysis). In between these two levels of EKR targets there is the so-called 'adequacy zone'.

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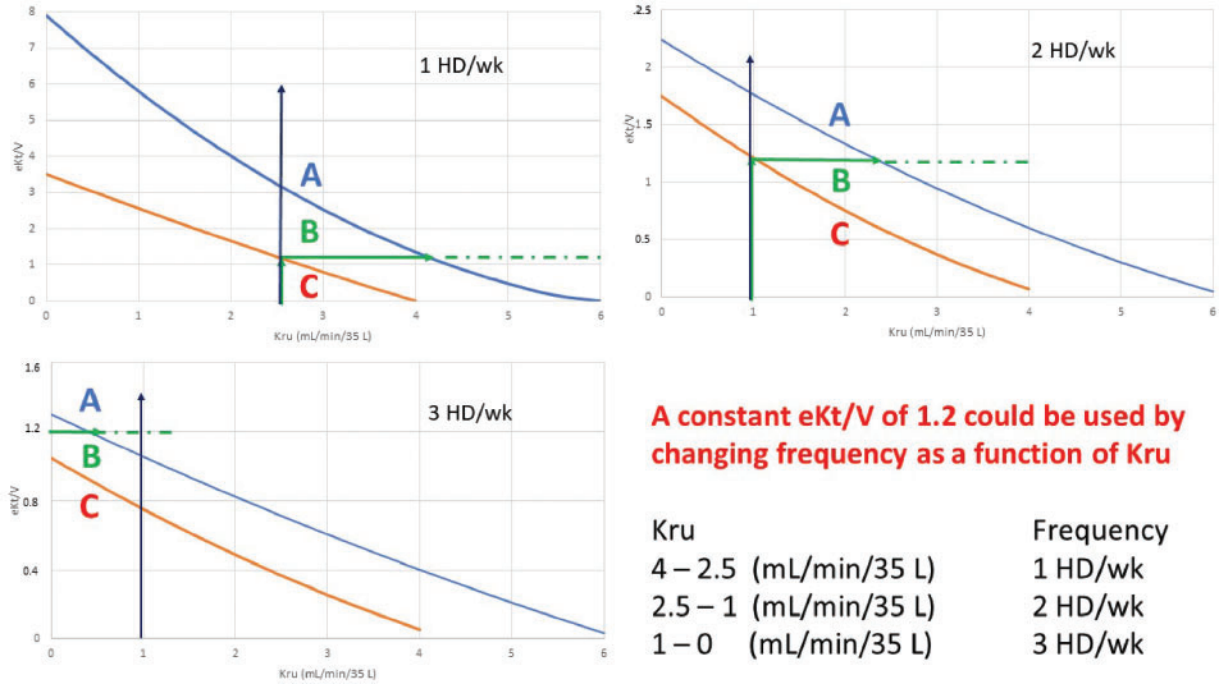

FIGURE A2: Adequacy map for the prescription of incremental HD by using a constant value of $eK_t/V = 1.2$ and changing the frequency of treatments as a function of Kru. The blue line in the three figures represents the equation that predicts the eK_t/V required to reach the highest target for EKR, as computed with $Y = 12 - \text{Kru}$, as a function of Kru on 1, 2 and 3 HD sessions per week, respectively. The orange line does the same for the lowest target $Y = 10 - 1.5 * \text{Kru}$. The letter 'A' represents an area of a probably excessive urea clearance; the letter 'C' represents an area of probable under-dialysis; the letter 'B' between A and C is an area of adequate urea clearance values. The horizontal green lines show that a constant eK_t/V of 1.2 per session could provide an adequate urea clearance for $2.5 < \text{Kru} < 4$ mL/min/35 L (actually <4.2) on 1 HD/week session, for $1 < \text{Kru} < 2.5$ mL/min/35 L on 2 HD/week sessions and $0 < \text{Kru} < 1.0$ mL/min/35 L (actually <0.5) on 3 HD/week sessions. The dashed green lines mean that the suggested eK_t/V of 1.2 is probably greater than needed, based on the Kru value on the abscissa; nonetheless, for the sake of simplicity, one could keep on using this eK_t/V value.

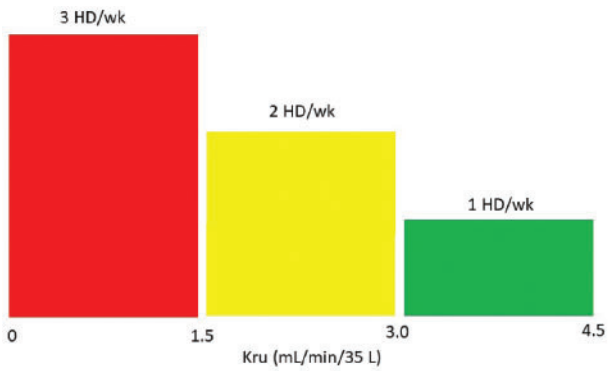

FIGURE A3: Rule of thumb for the prescription of incremental HD (based on VTM) is shown: a constant value of $eK_t/V = 1.2$ is used with frequency of treatments changing as a function of Kru. In order to increase the safety, the limits shown in Figure A2 have been shifted by 0.5 mL/min/35 L to the right.

respectively [59]. We can now use the two equations to design an adequacy map for the prescription of incremental HD based on the total EKR target we decided to choose (Figure A1): on one side (right side of the figure), the 'above target' EKR is shown; on the opposite side (left side of the figure), the 'below target' EKR is shown (potential risk of under-dialysis). In between these two levels of EKR there is the so-called 'adequacy zone', which corresponds to a Kru between 4 and 6 mL/min/35 L (i.e. a GFR between 6 and 9 mL/min/35 L). HD treatment should be started when Kru is between 4 and 6 mL/min/35 L.

It is possible to define three equations for the first (12 − Kru) and the second EKR target equation (10 − 1.5 * Kru) to predict the eK_t/V values to be delivered to the average patient to get the adequate EKR targets on 1, 2 and 3 HD/week schedules, respectively [59]. So that, by drawing the two lines, one can define three zones (Figure A2): A indicates the 'above target' eK_t/V; B indicates the 'target' eK_t/V; and C indicates the 'below target' eK_t/V. As shown in Figure A2, one could simplify the prescription by using a constant value of $eK_t/V = 1.2$ over an appropriate Kru interval. For further simplification and safety, one could shift the above values by 0.5 mL/min/35 L to the right so that the 'Kru thresholds for progression' become (Figure A3):

Kru ≥3 mL/min/35 L: 1 HD/week;
1.5 mL/min/35 L ≤ Kru <3.0 mL/min/35: 2 HD/week;
Kru <1.5 mL/min/35 L: 3 HD/week.

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